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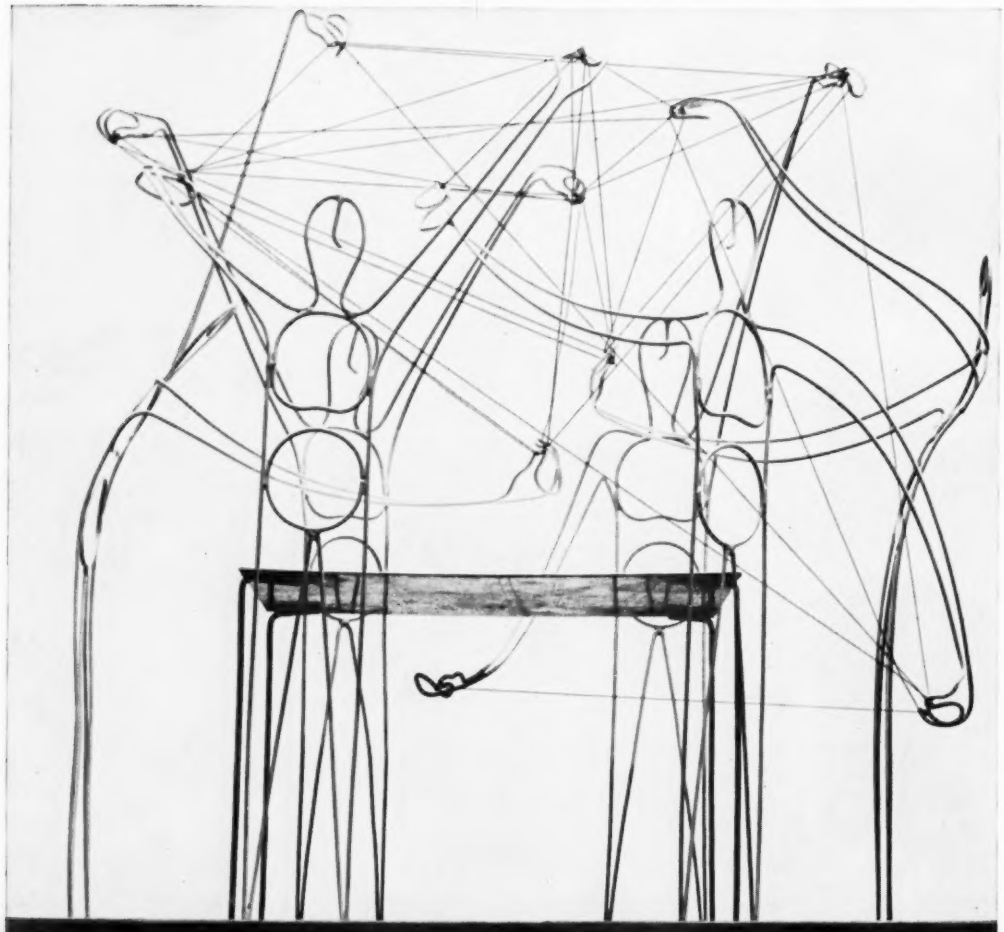

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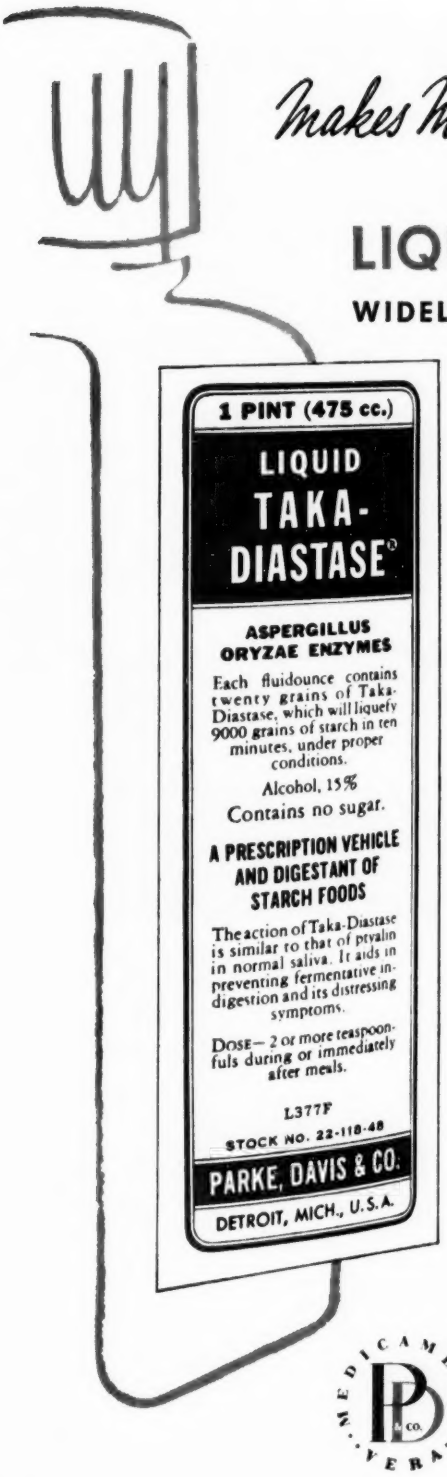
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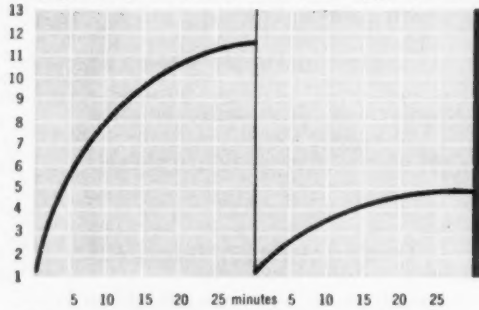

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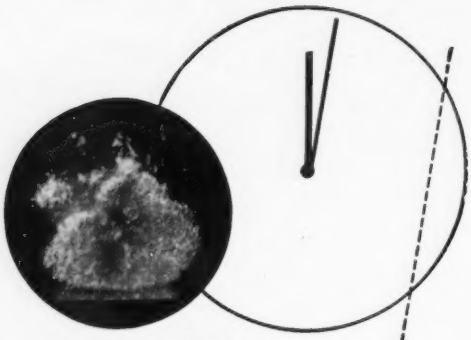

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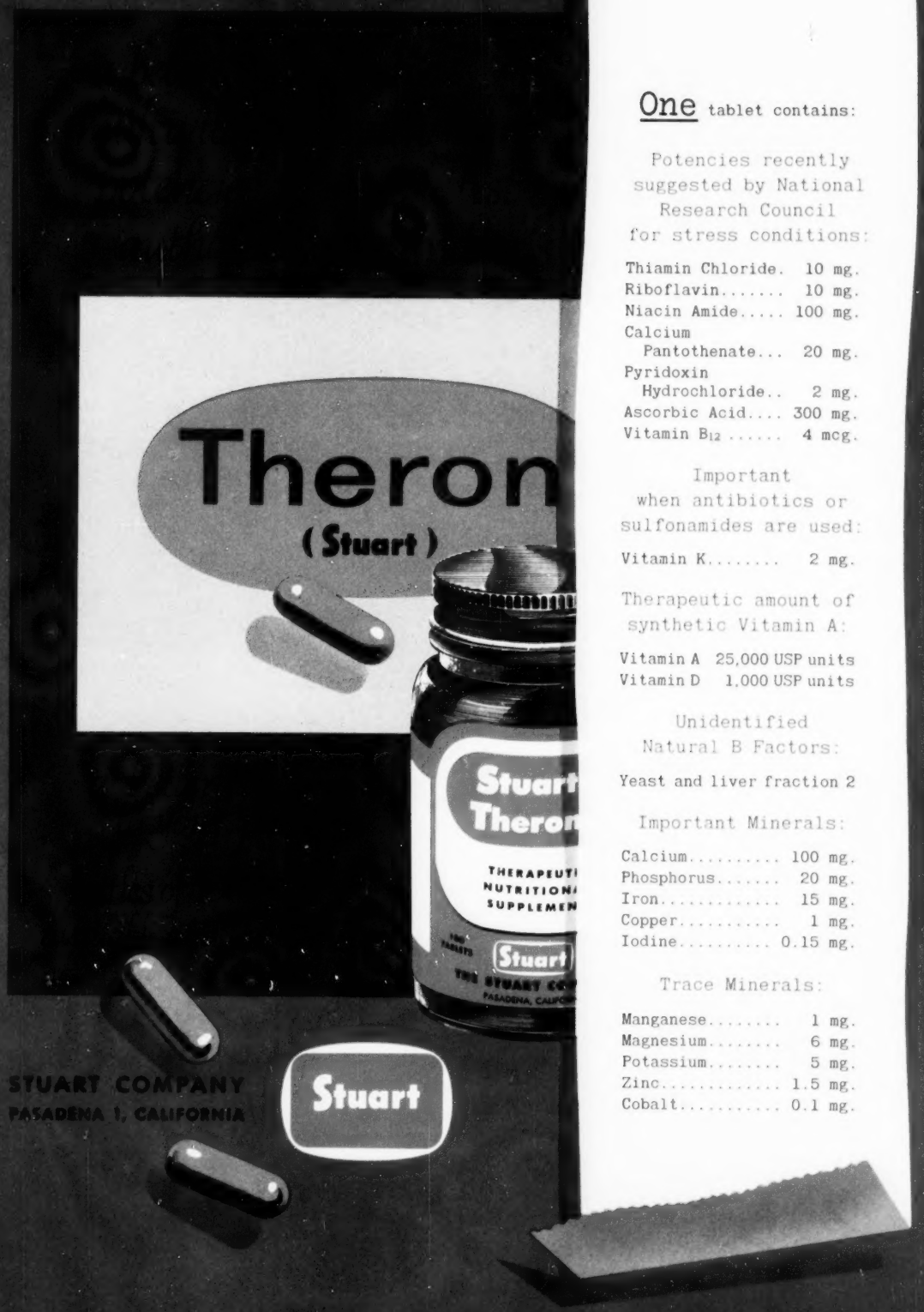

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HEMATOLOGIC STUDIES IN ATROPHIC GASTRITIS*

MORRIS E. DAILEY, M. D., MATTHEW J. ELLENHORN, M. D. AND ERNEST H. FALCONER, M. D.,
San Francisco, Calif.

THE PURPOSE of this study is to elucidate the hematologic changes associated with atrophic gastritis in patients who do not also have pernicious anemia.

Several investigators have reported that atrophic gastritis may be associated with pernicious anemia (1), hypochromic anemia (2), a deficiency of certain vitamins of the B-complex (3), sprue (4), or combined degeneration of the spinal cord (5). Although Hurst (6) and Konjetzny (7) believed that atrophic gastritis was the primary cause for the lack of formation of the anti-anemic principle and therefore was the cause of pernicious anemia, the association of pernicious anemia and atrophic gastritis is not universal. In our clinic, 13 of 25 treated patients (52 per cent) with pernicious anemia had no gastroscopic evidence of atrophic gastritis. Conversely, of 95 patients with atrophic gastritis, 12 (12.6 per cent) had pernicious anemia. Thus, the association of atrophic gastritis and pernicious anemia is far from a clear-cut cause and effect relationship.

Evidence that the mucosa of atrophic gastritis may become normal after treatment with liver extract was first obtained by Jones, Benedict, and Hampton (8). In their group of five patients with pernicious anemia, two showed unequivocal gastroscopic evidence of atrophic gastritis, but after successful treatment of the anemia with liver extract, the gastric mucosa appeared normal within two months in one patient and within five months in the other. Schindler and Serby (1) also indicated that gastric mucosal regeneration may occur in patients treated with liver extract. Schindler, Kirsner and Palmer (9) described eight patients with atrophic gastritis "not associated with pernicious anemia, combined cord degeneration, sprue, or pellagra"; in four the gastric mucosa appeared normal after administration of liver extract. Schiff and Goodman (10) found that Ventriculin® in a daily dosage of 30 to 60 grams apparently caused the reversion of an atrophic mucosa to normal. Atrophic gastritis recurred in two patients after the treatment was discontinued. Rodriguez-Olleros (4) also demonstrated by gastroscopic examination that an improvement in the atrophic gastritis occurred following the use of liver extract in patients with sprue. Abels (3) noted disappearance of atrophic changes in the gastric mucosa in three of eight patients following large doses of liver extract. Equivocal results after administration of liver extract to patients were noted recently by Findley, Kirsner and Palmer (11). Shapiro et al. (12) studied a group of 13 patients with atrophic gastritis in an attempt to discover evidence of vitamin deficiency and to ascertain the effect of the administration of specific vitamins. As a result of clinical and dietary studies, these authors concluded that nutritional deficiency occurred more frequently in their patients with atrophic gastritis than in a group of control subjects. Treatment with a variety of vitamins, however, had no effect on the gastric condition, although the atrophic gastritis disappeared in two of five patients treated with choline.

These investigations suggest that atrophic gastritis may be a clinical manifestation of a chemical deficiency which has not been clearly identified as yet. Furthermore, at present it is not known whether more than one substance is responsible for the changes observed in the gastric mucosa.

It is well known that anemia is frequently associated with abnormal gastric function. Thus, when gastric anacidity exists, absorption of iron may be inadequate and may result in a microcytic anemia. Gastric resection, especially if it results in malfunctioning enterostomies, may create a macrocytic anemia which may be exceedingly refractory to treatment. Conversely, anemia does not necessarily occur following total gastrectomy. The case which led to this study was that of a patient who had a chronic ileo-colitis, severe generalized atrophic gastritis, and a macrocytic anemia. Since loss of blood from the bowel was excluded, it was thought that perhaps inadequate absorption of anti-anemic principle caused the atrophic gastritis as well as the anemia.

MATERIAL AND METHOD

Fifteen patients were selected solely on the basis of the presence of atrophic gastritis without other disease of the stomach. The diagnosis of atrophic gastritis was established at gastroscopic examination by the pathognomonic finding of sizable areas of smooth gastric mucosa with distinctly visible, dark blue submucosal vessels. It is primarily the thinning of the mucosa that allows these vessels to become visible, although histologically demonstrable atrophic gastritis may occur without visibility of submucosal vessels at gastroscopic examination. The gastritis was generalized and pronounced in 11 patients and less extensive in four. None of the patients had pernicious anemia or presented evidence of infection, metabolic disease, or blood loss.

The age of the patients ranged from 20 to 72 years (average age—55.8 years). There were nine males and six females. Gastric analysis in 13 patients showed histamine-fast anacidity in 9 patients, anacidity after alcohol stimulation in one, and free hydrochloric acid in three.

Complete cytological analysis of the peripheral blood and examination of the bone marrow were made

*Aided by a grant from the Donner Foundation, Cancer Division, Philadelphia, Pa.

From the Department of Medicine of the University of California School of Medicine and the Gastrointestinal and Hematological Clinics of the University of California Hospital, San Francisco, California.

Submitted Nov. 19, 1952.

TABLE I.
PERIPHERAL BLOOD STUDIES IN ATROPHIC GASTRITIS

Case Number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	Average	Range
RBC (millions per cu. mm.) Normal: 4.0-5.5	4.73	4.36	4.58	4.83	4.90	4.85	4.30	5.22	3.20	5.12	4.97	4.20	4.37	4.64	2.70	4.47	2.70-5.22
Hemoglobin (Gm.%) Normal: 13-15	12.4	12.4	9.9	12.9	12.1	12.7	13.0	15.0	11.7	13.3	11.6	11.0	13.3	14.0	10.0	12.4	9.9-15.0
Packed cell vol. (cc.%) Normal: 42-50	44	36	39	43	40	43	41	46.5		47	36	38	46		29	40.7	29-47
WBC (per cu. mm.) Normal: 5,000-10,000	7500	9600	9000	8000	6100	5300	5100	10,400		11,000	10,600	13,100	24,800	4960	5100	9326	4960-24,800
Platelets (per cu. mm.) x 103 Normal: 350,000-550,000		390	380	420			480				400	450	370			412.8	370-480
Color Index Normal: 0.90-1.10	0.88	0.96	0.73	0.90	0.83	0.88	1.02	0.97	1.19	0.87	0.78	0.88	1.02	0.98	1.21	0.94	0.73-1.21
Mean Corp. Hgb. (γ) Normal: 27-33	26.2	28.5	21.7	26.8	24.6	26.1	30.1	28.7	36.6	25.9	23.3	26.2	30.3	30.2	35.8	28.1	21.7-36.6
Volume Index Normal: 0.95-1.05	1.06	0.94	0.97	1.02	0.93	1.01	1.09	1.02		1.04	0.84	1.03	1.20		1.23	1.03	0.84-1.23
Mean Corp. Vol. (cu. μ) Normal: 80-94	93	82	85	89	81	88	95	89		91	73	90	105		107	90	73-107
Mean Corp. Hgb. Conc. (%) Normal: 33-38	28.2	34.5	25.5	30.1	30.3	29.5	31.6	32.3		28.2	32.2	29.0	30.4		33.4	30.4	25.5-34.5
Saturation Index Normal: 0.87-1.13	0.83	0.97	0.75	0.88	0.89	0.87	0.93	0.95		0.83	0.92	0.85	0.85		0.98	0.88	0.75-0.98

soon after discovery of the atrophic gastritis. In all cases the bone marrow specimens were spreads from aspirated marrow stained with Jenner's polychrome dye and Giemsa's counterstain.

RESULTS

Analysis of the peripheral blood studies of the 15 patients gave the following results (Table I). The packed cell volume was within normal limits in six patients, below normal in seven; it was not determined in two patients. It was believed that seven of the patients had definite anemia, although it was severe in only three. The anemia was microcytic in four patients, normocytic in one, and macrocytic in two. The mean corpuscular volume was within normal limits in nine patients, increased in three, and decreased in one; it was not determined in two patients. The mean corpuscular hemoglobin was below normal in eight patients, above normal in two, and within the normal range in five. The mean corpuscular hemoglobin concentration was below normal in 11 patients and elevated in none.

Studies of the bone marrow showed no pronounced abnormalities of a consistent nature (Table II). A low percentage of lymphocytes, however, appeared to be a more or less common denominator. In seven patients the percentage of plasma cells in the marrow was increased. The erythroid distribution was normal in all the specimens of marrow. There was no evidence that lack of free hydrochloric acid in the stomach or the presence of atrophic gastritis was associated with any abnormality of erythroblastic proliferation.

DISCUSSION

The clinical data on this series of patients are recorded in Table III. It is noteworthy that four patients had a peripheral neuritis, in two of whom a diagnosis of combined system disease was considered. This fact might suggest that the presumed deficiency that causes atrophic gastritis also affects the nervous system.

It is our observation that atrophic gastritis produces no clinical symptoms which are pathognomonic of its presence, although Schindler and Murphy (13) have suggested that it may result in malaise, pronounced weakness, and occasionally glossitis. Gastric bleeding may occur in this disease, although it is rare.

Of primary significance is the fact that atrophic gastritis appears to be a precursor of certain gastric neoplasms, both benign and malignant. As evidence, Schindler (14) has shown that gastric polyps were present in 6 per cent of his patients with atrophic gastritis, but in only 0.83 per cent of patients with normal gastric mucosa. There is no evidence that polyps cause atrophy. Pernicious anemia is more frequently associated with gastric neoplasms than chance would allow. This point has been emphasized by Rigler et al. (15). They made radiologic examinations of the stomachs of 211 patients with pernicious anemia every six months and found gastric polyps in 15 patients and carcinoma in 17. Autopsy studies by Brown (16) disclosed ten epithelial polyps in 151 cases of pernicious anemia.

TABLE II

STERNAL BONE MARROW STUDIES IN ATROPHIC GASTRITIS

Case Number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Myeloblast															1.3
Promyelocyte	0.8	0.2	0.6	1.6	1.2	1.2	1.2		0.8	0.2		2.6	2.4		2.3
Myelocyte Neut.	3.8	7.8	15.0	6.2	5.6	6.4	8.4	8.2	6.2	5.2	10.6	10.4	10.6	4.0	11.3
Eosin.	0.8	1.2	8.8	1.6	3.6	2.0	4.6	4.0	4.0	4.4	2.0	2.4	2.0		1.7
Metamyelocyte Neut.	8.6	5.0	6.2	3.8	7.6	2.4	4.8	1.8	2.0	6.2	2.2	5.4	7.6	6.2	13.0
Eosin.															1.7
PMN Neut. N. F.	39.6	33.6	25.6	15.4	28.0	38.0	34.4	35.6	36.2	26.0	48.2	41.0	27.6	31.6	36.3
Fil.	5.4	6.4	1.4	1.4	1.2	2.0	3.6	6.0	2.0	0.6	6.0	5.0	1.0	6.6	8.7
Eosin.	0.2	2.0	2.6	0.8	0.8	0.6	0.2	2.4	2.4	4.6	2.8		1.6	3.6	1.3
Baso.	0.6				0.2	0.4									0.7
Lymphocyte	3.0	3.4	2.4	2.2	3.2	1.0	1.4	4.4	1.0	2.0	3.2	1.6	0.8	7.4	3.7
Promonocyte												0.2			
Monocyte	3.8	2.0	2.2	3.8	8.2	7.4	7.8	4.4	2.4	6.0	1.8	4.4	2.0	2.6	0.7
Plasmacyte	2.4	4.2	2.8	5.6	2.4	0.4	1.6	1.6	0.6	4.0	0.8	1.8	5.6	1.8	1.7
Megaloblast	1.0		0.8		0.6	1.2	1.0		1.4	0.8			0.2		1.0
Proerythroblast	3.4	1.0	3.6	4.2	3.6	3.0	5.2	0.4	5.6	3.4	0.8	3.6	2.8	0.8	
Erythroblast	22.8	30.6	24.2	45.6	28.4	33.8	24.0	29.6	34.0	29.4	20.8	20.2	33.8	34.4	13.0
Megakaryocyte	0.4		0.8	0.2		2.0				0.2	0.8		0.2	0.4	
Histiocyte	3.4	2.6	0.4	6.6	4.2	1.4	1.4	0.8	0.8	6.4		1.4	0.6	0.6	
Primitive R-E Cells			2.6												
Mitotic Cells				1.0	1.2	0.6	0.4	0.8	0.6	0.6			1.2		1.0

Previously, the same number of polyps was found by Ophüls (17) in his series of 3000 routine autopsies.

It is of interest that of 54 patients with atrophic gastritis proved by gastroscopic examination, Findley et al. (11) in a follow-up study five years later found that none had developed pernicious anemia. Except for one woman who had become mildly anemic, all patients whose blood counts were measured showed more than 3,900,000 red blood cells per cubic millimeter, and more than 12.0 grams percent concentration of hemoglobin.

SUMMARY

Study of the peripheral blood and of smears of the sternal bone marrow of 15 patients with atrophic gastritis without pernicious anemia revealed no consistent abnormalities which might aid in identifying the cause of the gastric disease. A mild anemia, predominantly microcytic or macrocytic, was observed in seven patients.

Definition of the causes of atrophic gastritis would be desirable since this condition appears to be the soil in which certain gastric neoplasms develop.

TABLE III

CLINICAL SUMMARY OF CASES OF ATROPHIC GASTRITIS

Case Number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Age	42	59	20	43	69	68	38	48	55	72	46	70	56	55	72
Free Hcl* (Gastric)	O_H	O_H	O_H		O_H	O_H	O_A	+		+	O_H	+	O_H	O_H	O_H
Neurological Symptoms	O	+	O	+	O	O	O	O	O	O	O	O	+	O	+
Degree of** Gastric Atrophy	G-4	NG-4	G-4	G-4	NG-3	G-4	G-3	G-4	G-4	G-4	G-3	NG-4	G-4	NG-3	G-3

*H—Histamine Test
A—Alcohol Test
O—Anacidity

**G—Generalized
NG—Not generalized
1-4—Degree of severity

REFERENCES

1. Schindler, R. and Serby, A. M.: Gastroscopic observations in pernicious anemia. Arch. Int. Med., 63:334, 1939.
2. Chevallier, P. and Moutier, F.: La gastroscopie dans les maladies du sang. Sang, 11:935, 1937.
3. Abels, J. C.: Cited by Shapiro et al. (12).
4. Rodriguez-Olleros, A.: The stomach in tropical sprue. Puerto Rico J. Pub. Health and Trop. Med., 13:503, 1938.
5. Palmer, W. L. and Porter, R. T.: Combined cord degeneration without anemia: a case report with studies bearing on the "intrinsic factor" of Castle. J. Clin. Invest., 15:343, 1936.
6. Hurst, A. F.: The unity of gastric disorders. Brit. Med. J., 2:89, 1933.
7. Konjetzny, G. E.: Die Entzündung des Magens. In Henke-Lubarsch: Handbuch d. pathol. Anatomie, 4:Heft 2. Berlin, Springer, 1928.
8. Jones, C. M., Benedict, E. B., and Hampton, A. O.: Variations in the gastric mucosa in pernicious anemia: gastroscopic, surgical, and roentgenologic observations. Am. J. M. Sc., 190:596, 1935.
9. Schindler, R., Kirsner, J. B., and Palmer, W. L.: Atrophic gastritis: gastroscopic studies on the effects of liver and iron therapy. Arch. Int. Med., 65:78, 1940.
10. Schiff, L. and Goodman, S.: Desiccated hog's stomach extract (Ventriculin) in the treatment of atrophic gastritis. Am. J. Digest. Dis., 7:14, 1940.
11. Findley, J. W., Jr., Kirsner, J. B., and Palmer, W. L.: Atrophic gastritis: a follow-up study of 100 patients. Gastroenterology, 16:347, 1950.
12. Shapiro, N., Schiff, L., Bloch, H. S., Garber, E. S., and Hannaher, M. J.: Some observations on specific vitamins and atrophic gastritis. Gastroenterology, 2:121, 1944.
13. Schindler, R. and Murphy, H. M.: Symptomatology of chronic atrophic gastritis. Am. J. Digest. Dis., 7:7, 1940.
14. Schindler, R.: Gastritis, New York, Grune and Stratton, 1947.
15. Rigler, L. G., Kaplan, H. S., and Fink, D. L.: Pernicious anemia and the early diagnosis of tumors of the stomach. J.A.M.A., 128:426, 1945.
16. Brown, M. R.: Pathology of gastro-intestinal tract in pernicious anemia and subacute combined degeneration of the spinal cord. Study of 151 autopsies. New England J. Med., 210:473, 1934.
17. Ophüls, W.: A Statistical Survey of Three Thousand Autopsies. Stanford University, Calif., Stanford University Press, 1826.

MASSIVE RESECTION OF THE SMALL INTESTINE: A SIX YEAR FOLLOW-UP STUDY

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IN A previous communication (1) one of us (J.K.B.) reported the case of a 51 year old, 200 pound woman, who had been taking large doses of ergot to control uterine bleeding. She was admitted to the Gynecology Service of the Indianapolis General Hospital on December 27, 1946, because of menorrhagia due to uterine fibromyomas. The family physician stated that the patient had what appeared to be a coronary occlusion in 1941 and that her blood pressure had remained at about 270 systolic, 150 diastolic since that time. These findings were confirmed on admission. Approximately 24 hours after she entered the hospital she developed thrombosis of the superior mesenteric artery with massive infarction of the intestine. The cecum, ascending colon (10 centimeters) and the entire small intestine (539 centimeters) except for the duodenum and 45.7 centimeters of the jejunum were resected. Continuity was re-established by end to side anastomosis between the proximal jejunum and the hepatic flexure of the colon. The patient had what might be termed a stormy postoperative course. However, by the fourth day she was placed on the following diet: beef broth, gelatin (Jello), custard, cottage cheese, milk, pablum, and a hydrolysate mixture. On January 18, 1947, 21 days after surgery, she was permitted a regular soft diet. Bowel movements averaged four to five per day, and the stools were partially formed. She was released from the hospital on the 29th of January, 1947, 32 days after surgery and she was advised to return to the Outpatient Department at weekly intervals.

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From the Departments of Surgery and Medicine, Indianapolis General Hospital. This study was aided by a grant from the Charles J. Wolf Foundation for Medical Research. Paul Fouts, M.D., and Woodson Young, M.D., gave many helpful suggestions in the care of this patient.

Since her release she has been readmitted to the hospital on two occasions. The first was because of vaginal bleeding due to uterine fibroids. On September 18, 1947, x-ray therapy was instituted with good results, and there has been no bleeding since that time. On April 8, 1950, she was asked to come into the hospital for a complete check-up and this will be discussed later in this paper.

In general, her complaints as an outpatient have been frequent stools, gaseous distention, flatulence and some weakness. Stools averaged twelve to fifteen per day and caused rectal irritation, tenesmus and anal discomfort, which was described by the patient as a constant burning sensation. Various suppositories and analgesics and emolients failed to relieve her. At times during the first year following surgery, the stools were bright yellow and foamy. However, occasionally they were semi-solid and brown. The diarrhea was invariably increased by the ingestion of sweets, fatty foods and large quantities of water. On the contrary, a low fat or fat free diet reduced the number of stools and the rectal-anal irritation.

In June 1949 a demulcent, (sorbitan mono-oleate polyoxyethylene derivative) was started in daily doses of 9 grams to promote fat metabolism. However, this failed to control the diarrhea. Her eating habits were as follows: she stated that she consumed three meals per day of normal amounts but ate very little

TABLE 1

MASSIVE RESECTION OF THE SMALL INTESTINE

Date	Hemoglobin in Percent	Erythrocytes in Millions	Leucocytes	Hematocrit	Reticulocytes
1-28-47	89.0	5.02	13,000		
3-25-47	87.0	4.55	6,800		
9-18-47	90.0	4.260	9,050	41.	
5- 3-48	70.5	3.80	5,300		
7-19-48	81.9	3.65			
2-30-49	71.5	2.320	3,200		
4- 6-50	70.5	2.56	2,000		
4- 8-50	67.9	2.2	2,900		0.8%
Vitamin B_{12} started 5 micrograms per day					
5-19-50	87.7	4.33			19.7%
5-24-50	83.1	4.70			2%
5-26-50	89.1	4.36			
5-31-50	89.1	4.39			
6- 7-50	86.1	4.45			
6-14-50	89.8	5.09			
6-23-50	96.0	4.44			
7-21-50	98.0	4.56			
8-18-50	87.8	4.56			
9-29-50	90.3	3.96			
11-3-50	92.8	4.56			
1- 1-51	87.8	4.88			
2-21-51	85.4	5.06			
4-27-51	98.0	4.66			
6-29-51	93.5	4.78			
7-21-51	98.0	4.86			
9- 7-51	97.3	5.30			
10-26-51	102.7	4.68			
1-18-52	97.3	4.35			
2-22-52	94.3	5.34			
3-28-52	92.3	5.32			
4-25-52	99.5	4.94			

between meals and that she carefully avoided sweet foods, fatty foods of any kind including cream in her coffee, and drank very little water. Her weight remained about the same, ranging from 146 to 160 pounds, although her preoperative weight was over 200.

Although her blood pressure before surgery was 270/150, by 1947 the highest pressure was 175/95 and at this time her weight was 160 pounds. Throughout 1948 and 1949 the blood pressure was never above 150/90.

Hemoglobin and erythrocyte counts remained normal until May 1948 when it was noted that the hemoglobin was 70.5% and the red blood cells 3.8 millions. In April 1950 the hemoglobin remained the same but the erythrocyte count fell to 2.56 millions. (See Table 1). A sternal puncture at this time showed a megaloblastic bone marrow similar to that seen in pernicious anemia. Gastric analysis disclosed a fasting pH of 6.9 and after histamine stimulation the pH was 8.0 in each of the three succeeding specimens. No free acid was found. Other laboratory work as an outpatient included determinations of total protein, albumin, globulin, chlorides, CO_2 and N.P.N. These determinations were all within normal limits. The intravenous and oral glucose tolerance tests showed rather flat curves. (See Table 2.)

On April 8, 1950 the patient was readmitted to the hospital complaining of extreme weakness, continual diarrhea of twelve to fifteen loose stools a day associated with gastric distention and rectal irritation at all times. Five weeks prior to her admission she complained of a persistent soreness of her tongue. A few white blisters were noted occasionally but they disappeared within two or three days. There was never any jaundice although she complained of a slight tingling or itching sensation in her hands and feet, especially when they were cool.

Physical examination showed the following interesting findings: her blood pressure was 140/90 in both upper extremities. The pulse was 76 and regular. She was afebrile and fairly well nourished. The conjunctiva, ear lobes, nose and throat were pale and the sclera were mildly icteric although the ophthalmologic examination revealed normal discs with a grade one sclerosis. The papillae of the tongue were definitely atrophic, and the mucous membrane of the rectum was pale and smooth and resembled that of atrophic glossitis and stomatitis. This was demonstrated by biopsies taken from the tongue, buccal and rectal mucosa. The chest and abdominal examinations were normal except for the well healed right paramedian scar. Extremities were not edematous, however, it was noted that the right leg was slightly larger than the left due to an old thrombophlebitis following pregnancy. Peripheral pulsations were present in all palpable arteries. Neurological examinations were entirely normal. Deep and superficial reflexes were equal bilaterally; position sense was intact and vibratory sensibility was normal. No pathologic reflexes could be demonstrated.

Laboratory findings at this time were as follows: Hemoglobin 67.9%, erythrocyte count 2.2 millions, leucocytes 2,900, reticulocytes 0.8% and sedimentation rate 6.0. The hematocrit was 38 and both oral and intravenous glucose tolerance curves were flattened. The maximum blood sugar on the oral glucose tolerance curve was 99 milligrams per cent at ½ hour. With the intravenous glucose tolerance test the maximum increase was 106 milligrams per cent in ½ hour. An xylose absorption test showed a total of 2.76 grams of xylose excreted in the urine in five hours. The maximum blood level was 16.7 milligrams per cent at one hour. These findings are compatible

TABLE II

MASSIVE RESECTION OF THE SMALL INTESTINE

Date	Total Protein	Albumin	Globulin	Serum Cholesterol	Chlorides	N. P. N.
1-27-47	7.9	4.0	3.9			
2-26-47	5.4			167 mg. %	670	33
3-25-47	6.5	3.8	2.7	185 mg. %	715	36
9-22-47	6.6	3.9	2.7			
5- 3-48	6.68	4.02	2.66		700	
3-14-49	7.1	4.4	2.7			30
6-10-49	6.2	3.8	2.4			30
4-11-50	6.0	4.06	1.97	79 mg. %		
7-13-50				119 mg. %		
6-13-52	7.41	4.78	2.63	156 mg. %		

INTRAVENOUS GLUCOSE TOLERANCE TEST USING 25 GRAMS GLUCOSE

Date	Fasting Blood Sugar	½ Hour	1 Hour	2 Hours	3 Hours
6-9-49	70 mg.%	98 mg.%	63 mg.%	51 mg.%	61 mg.%
4-13-50	86 mg.%	106 mg.% maximum	82 mg.%	59 mg.%	72 mg.%

ORAL GLUCOSE TOLERANCE TEST

Date	Fasting Blood Sugar	½ Hour	1 Hour	2 Hours	3 Hours
6-10-49	71 mg.%	95 mg.%	85 mg.%	85 mg.%	69 mg.%
4-10-50	77 mg.%	99 mg.% maximum	89 mg.%	72 mg.%	83 mg.%

GASTRIC ANALYSIS WITH HISTAMINE STIMULATION

Date	Fasting pH	20 minutes	40 minutes	60 minutes
4-6-50	6.9	8.0	8.0	8.0
6-6-52	7.35	1.35	1.60	1.70

with decreased absorption of xylose from the gastrointestinal tract. Total protein was 6.03 grams per cent; albumin 4.06 grams; globulin 1.97 grams; and the albumin-globulin ratio was 2.06. Two hour quantitative urine urobilinogen revealed 0.37 Ehrlich units. Serum cholesterol was 79 milligrams per cent; serum bilirubin 1.05 milligrams per cent; thymol turbidity 2 units; cephalin flocculation 24 hours negative, 48 hours 1 plus; bromsulfthalein 30 minutes 3.5% retention, 45 minutes 0.38% retention.

X-ray films of the chest were entirely normal. There was a normally functioning gallbladder without evidence of stones. Barium enema was normal and revealed no evidence of an obstruction. However, barium did not enter the jejunum by retrograde methods. Barium given by mouth showed a normal stomach, esophagus and duodenal bulb. There was a small diverticulum of the second portion of the duodenum. The barium passed rapidly through the surgically shortened small and large intestine reaching the transverse colon within 40 minutes. Most of the meal was in the descending colon within 90 minutes. X-ray examination of the pelvis and long bones showed no changes of an osteosclerotic nature. The electrocardiograms were entirely normal. Biopsy of the tongue and rectum at this time showed an atrophic glossitis and atrophic proctitis.

Because of the megaloblastic condition of the sternal marrow, the absence of free acid in the gastric juice, the anemia and severe glossitis and weakness, the impression on admission was that the patient was suffering from pernicious anemia or at least a macrocytic anemia due to nonabsorption of food. Consequently the patient was started on 5 micrograms of B_{12} intramuscularly per day and she had a maximum reticulocyte response from this treatment of 19.7% on the eighth day. At the time of her release her hemoglobin had increased to 92.3% and her erythrocytes to 4.14 millions and the reticulocytes were 2%. The patient continued to receive 15 micrograms of Vitamin B_{12} by injection twice weekly.

Her improvement was remarkable. The stools assumed a normal consistency and were reduced to approximately four to five per day. Irritation of the rectum disappeared and a tongue and rectal biopsy several months later revealed a normal glossal and rectal mucosa. Her general improvement was equally remarkable because of an increase of appetite and strength. She has remained on a fat-free diet, high in carbohydrates and proteins.

Since her release from the hospital in June of 1950 all laboratory work including hemoglobin, erythrocyte counts, total protein, albumin, globulin, albumin-globulin ratio, and cholesterol have been within normal limits. On June 6, 1952 a repeat gastric analysis with histamine stimulation showed a fasting pH of 7.35 with a pH of 1.35, 1.60 and 1.70 in each of the three succeeding specimens. This rules out pernicious anemia but it is difficult to explain the findings before the institution of vitamin B_{12} therapy. We are forced, however, to conclude that this represents a case of macrocytic anemia due to malnutrition. Also it should be noted that after the correction of anemia the blood pressure has increased to 200 systolic over 100 diastolic.

Discussion

Massive resection of the intestine refers to resection of more than 200 centimeters or an average of one-third of the small intestine. This in the early experimental work of Senn (2) represents the length of the small intestine which may be safely removed in experimental animals.

The first case of massive resection was reported by Koeberle (cited by Haymond (5)) when he removed 205 centimeters of small intestine from a man injured in an accident. In 1881 Kocher (3, 4) took out 208 centimeters of small bowel and since that time more than 350 cases of massive resection of the small intestine have been reported. Haymond (5) collected and summarized 257 cases in 1935 and an attempt was made at that time to determine the amount of intestine which could be resected safely without subsequent morbidity. Although no definite conclusions could be drawn from this study, Flint (6) in 1912 stated that the metabolic disturbances were proportional to the amount of intestine remaining and not the amount resected. Also, he called attention to the fact, as we had done in our previous paper, that there is great variation in the length of the small intestine. Bryan (7) in a summary of 160 adults showed that the length of the intestine varies from 10 feet to 28 feet 4 inches. Haymond concluded in his summary that 33% of the small intestine might be removed without any serious metabolic alterations. However, if 50% is resected one could expect severe disturbance.

Numerous cases of massive resection of the small intestine have been reported since Haymond's review (8-33 inc.). Our patient represents one of the longest survivals in a case with only 18 inches or 45.7 centimeters of small bowel and only about 150 centimeters of large bowel remaining. Haymond reported two cases with much less resection than ours which had been followed for 18 years. Three other cases of survival following the resection of all but 18 inches of the small intestine have been reported (19, 24, 29) and one (20) reported a seven month follow-up study in a patient with only 14 inches of small intestine and all of the colon remaining. Chodoff's (25) case with 8" of jejunum and ileum and all of the large bowel remaining died 7 months postoperatively of congestive heart failure. Wilkie (28) reported an 18 month follow-up study of a case with 7 inches of the proximal jejunum, the distal ileum and all of the colon remaining. He concluded that because of the patient's severe weight loss, diarrhea and poor general condition, between 7 and 14 inches of small intestine is necessary to maintain normal physiology. Shonyo's case (27) had an adenocarcinoma of the jejunum requiring resection of all but 8.9 centimeters of the jejunum and a 2.5 centimeter segment of the ileum totalling 11.4 centimeters of small intestine. The patient expired 18 months after resection from metastases.

The chief metabolic disturbances reported with massive resections have been as follows: intractable diarrhea resulting in great loss of weight due to excessive loss and lack of absorption of fats and proteins. Metabolic studies by Flint (6) in 1912, West (8) in 1938 and Todd (10) in 1940 showed that carbohydrates were utilized normally. However, approximately 45% of the ingested fats and 25% of the ingested proteins were lost in the stool. The intestinal contents revealed much fatty acid indicating good digestion but improper absorption of fats. Also, there is an excessive loss of calcium with the ingestion of more fat in the diet. The patient reported by West and Todd had episodes of tetany which were controlled by the administration of calcium and Vitamin A. Cosh (16) also reported a case of tetany after extensive resection of the intestine and in 1949 Althausen (24) and his associates reported metabolic studies on a patient with only 45 centimeters of small intestine remaining. They compared the utilization of food from a "natural" versus a "synthetic" diet. Both diets contained 1610 calories. The synthetic diet which contained 75 grams of protein hydrolysates, 180 grams of 20% cream, and 176 grams of glucose with 240 cc. of whole milk flavored with cocoa was no better digested than natural foods containing 90 grams of protein, 50 grams of fat and 200 grams of carbohydrates. In fact 18% more nitrogen was lost in the feces in a synthetic than from a natural diet. In a patient studied by Berman and associates (29) with only 18" of jejunum and no large bowel remaining (the patient had had an abdominoperineal resection for cancer of the rectum nine years previously), metabolism of fat and protein were similar. Both of the patients remained in a positive nitrogen balance in spite of the absorption of only approximately 50% of the nitrogen. Berman's patient had an intractable diarrhea which was unresponsive to all drug therapy including tincture of opium, paregoric, bismuth, atropine, belladonna, "dreft" aluminum hydroxide, apple powder and psyllium seed. However, her diarrhea responded slightly to a fat-free diet. Christensen and his associates (30) reported observations of gastrointestinal function in a patient in whom 220 centimeters of ileum and 45 centimeters of the proximal colon were removed. Their studies five months postoperatively revealed that the patient lost five times the normal amount of fat which is lost in the stools, but that 80% of the fat was absorbed. These observations revealed a large reserve capacity of the small intestine. They also noted that in their patient, protein hydrolysates actually increased the diarrhea and also the loss of nitrogen. We had the same experience in our patient. "Tween 80," the same demulcent which was used in our case failed to improve the absorption of fat in their patient.

We have found no report of macrocytic anemia occurring in a case of massive resection of the small intestine with resection of the ascending colon. Experimentally in rats with massive resections where 40 or 80% of the jejunum and ileum are removed, anemia develops very slowly. However, the anemia is always hypochromic. At no time is there a significant macrocytic anemia present. The work of Barker and Hummel (34) concerning macrocytic anemia and intestinal strictures indicated that the macrocytic anemia which follows intestinal stricture can frequently be corrected by massive resection. Some observers (35) have stated that macrocytic anemia does not seem to be a sequel of massive resection as is sometimes the case in short circuiting operations or in strictures of the intestines. The anemia in our case developed slowly and was probably due to malnutrition based upon poor absorption of food. The administration of B_{12} not only corrected the anemia but markedly improved the bowel function so that the stools were reduced to approximately four or five per day. There was also an improvement in the mucosa of the tongue and of the rectum. This leads one to speculate whether or not the diarrhea in massive resection may actually be due to an atrophic proctitis with its irritating effects. These observations may indicate that B_{12} is

an important factor in controlling the intractable diarrhea following massive resection.

The reduction in blood pressure may be related to several factors. The patient weighed approximately 200 pounds on admission to the hospital and had a blood pressure of 270/150. However, postoperatively her weight remained between 140 and 160 pounds. Her systolic blood pressure at this time also was lower and stayed at about 175 millimeters of mercury until after the anemia was corrected, then her weight remained about the same but the blood pressure rose again to 200 systolic and 100 diastolic.

CONCLUSIONS

1. We have presented a six year followup study of a patient upon whom one of us (J. K. B.) performed massive resection of all of the jejunum except for 45.7 centimeters, the ileum and the ascending colon.

2. A macrocytic anemia developed very slowly producing weakness, atrophic glossitis and proctitis and a paresthesia of the hands and feet. This responded well to the administration of vitamin B_{12}. Macrocytic anemia in patients with massive resection has not been reported to our knowledge.

3. The persistent and continual diarrhea responded dramatically to the administration of Vitamin B_{12}.

4. The low blood pressure which the patient developed following her surgery was probably caused in part by the macrocytic anemia, because the blood pressure has now become elevated again after the correction of the anemia with Vitamin B_{12}.

5. Metabolic studies on experimental animals and in those cases of massive resections reported in the literature indicate poor absorption of fat and protein.

REFERENCES

1. Berman, J. K., Brown, H. M., Foster, Ray T., and Grisell, T. L.: Massive Resection of the Intestine, J. A. M. A., Vol., 135, pp 918-19, Dec. 1947.
2. Senn, Nicholas: An Experimental Contribution to Intestinal Surgery with Special Reference to the Treatment of Intestinal Obstruction. Annals of Surgery, Vol. 7 no. 1, 1888.
3. Elliott, J. W.: Operative Relief of Gangrene of the Intestine Due to Occlusion of Mesenteric Blood Vessels. Annals of Surgery, Vol. 21 No. 9, January, 1895.
4. Kocher, E. T.: Bull. de l'Acad. de Med. 1881, No. 4; cited by Elliot (3).
5. Haymond, H. E.: Massive Resection of the Small Intestine. Collection of 257 cases. S. G. & O., Vol. 61, page 693, 1935.
6. Flint, J. M.: Effect of Extensive Resection of the Small Intestine. John Hopkins Hosp. Bull. 23, page 127, 1912.
7. Bryant, John: Observations upon the Growth and the Length of the Human Intestine. J. A. M. Med. Science 167:499, 1924.
8. West, E. S. et al.: Digestion and Absorption in a Man with Only Three Feet of Small Intestine. Am. J. Digestive Diseases 5:690, 1938.
9. Whittaker, L. D. and Pemberton, J. deJ: Mesenteric Thrombosis. J. A. M. A., Vol. 111, page 21, 1938.
10. Todd, W. R. et al.: Digestion and Absorption in a Man with All but Three Feet of Small Intestine Removed Surgically. Am. J. Dig. Dis., Vol. 7, page 295, 1940.
11. Bowen, W. L.: Massive Resection of the Small Intestine. Am. J. Surgery, Vol. 58, page 438, 1942.
12. Coleman, E. P. and Bennett, D. A.: Massive Intestinal Resection. Am. J. Surgery, Vol. 59, page 429, 1943.
13. Hollman, L. L.: Survival After Removal of Twenty Feet of Intestine. The Lancet, Vol. 2, page 597, 1944.
14. Prioleau, W. H.: Massive Resection of the Small Intestine. Ann. Surgery, Vol. 119, page 372, 1944.
15. Cattell, R. B.: Resection of the Small Intestine. Lahey Clinic Bull. 4:167, 1945.
16. Cosh, J. A.: Tetany After Extensive Gut Resection. The Lancet, 2:596, 1944.
17. Elman, R. and Read, J. A.: Nutritional Recovery Following Removal of All but Three Feet of Jejunum and Half of the Colon. J. Missouri M. A. 42:145, 1945.
18. D'Albreu, F. and Humble, J. G.: Mesenteric Venous Thrombosis. Recovery after Resection with Hymein. The Lancet, Vol. 1:543, 1946.
19. Meyer, H. W.: Acute Superior Mesenteric Artery Thrombosis. Recovery Following Extensive Resection of the Small and Large Intestine. Archives Surgery, 53:298, Sept. 1946.
20. Cogswell, H. D.: Massive Resection of the Small Intestine. Ann. Surgery 127: 377, 1948.
21. McClinahan, J. E. and Fisher, Bernard: Massive Resection of the Small Intestine. Surgery 23:778, 1948.
22. Dempsey, W. S. and Jones, T. E.: Venous Mesenteric Thrombosis. Report of a Case with Recovery. Cleveland Clinic Quart. 15:140, 1948.
23. Goldman, A. M., Rives, J. D.: A Case of Mesenteric Venous Thrombosis with Survival. Ann. Int. Medicine 31:329, 1949.
24. Althausen, T. L., Uyeyama, K., Simpson, R. G.: Digestion and Absorption after Massive Resection of the Small Intestine. Utilization of Food from a "Natural" vs. a "Synthetic" Diet and a Comparison of Intestinal Absorption Tests with Nutritional Balance in a Patient with only 45 CM. of Small Intestine. Gastroenterology 12:795, May, 1949.
25. Chodoff, R. J.: Mesenteric Vascular Occlusion. Case Report of Successful Resection of All but 8 Inches of Jejunum and Ileum. Am. Surgery 131:440, March, 1950.
26. McClinahan, J. E., Fisher, Bernard: Physiologic Effect of Massive Small Intestinal Resection and Colectomy. Ann. J. Surgery 79:5, May, 1950.
27. Shonyo, E. S., Jackson, J. A.: Massive Resection of the Small Intestine. Report of a Case. Arch. Surgery, 61:1, July, 1950.
28. Wilkie, W.: Massive Resection of the Small Gut. Report of a Case. S. Africa Med. J. 24:26, July 1, 1950.
29. Berman, L. G., Ulevitch, H., Haft, H. H., Lemish, Sonia: Metabolic Studies of an Unusual Case of Survival Following Resection of all but 18 Inches of the Small Intestine. Annals Surgery, 132:1, July, 1950.
30. Christensen, N. A., Musgrove, J. E., Wollager, E. E.: Extensive Resection of the Bowel for Occlusion of the Superior Mesenteric Artery: Report of a Case with Postoperative Studies of the Function of the Gastrointestinal Tract. Proc. Staff Meetings of the Mayo Clinic, 25:16, Aug 2, 1950.
31. Koon, E. S., Jr.: Mesenteric Vascular Occlusion: Extensive Resection of the Small Bowel with Survival. J. A. M. A. 143:16, 19 August, 1950.
32. Kruger, E.: Venous Mesenteric Thrombosis (Report on a Case with Recovery). South African Medical Journal 26:4, 26 Jan. 1952.
33. Alt, Howard L.: Extensive Resection of the Small Intestine in the Rat with Special Reference to Anemia. Am. J. D'gest Dis. 3:169, 1936.
34. Barker, W. H., Hummel, L. E.: Macrocytic Anemia and Intestinal Strictures. Bull. Johns Hopkins Hospital 64:215, 1939.
35. Annotations: Massive Resection of the Small Intestine. The Lancet 2:606, 1949.

COMPATIBLE HYPERGLYCEMIA

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Part I. a. A New Mode of Diabetic Control.

b. Its relationship to other schools for guidance of Diabetic Therapy.

c. Effect of compatible Post Prandial Hyperglycemia upon insulin dose, apparent duration of diabetes and arteriovascular degeneration.

SINCE OUR first publication in 1937 (1), of the significance of postprandial blood sugar level in helping to guide our diabetic therapy, we have had innumerable inquiries concerning its interpretation. In subsequent publications (2-6) we attempted to clarify this latter point further, whereas the present investigations are the results of our more intensive studies of post prandial blood sugar levels, as well as of the relationship of vascular degeneration to blood sugar level, insulin dose and apparent duration of diabetes.

Since most of the physicians are in agreement that the blood sugar level is an index to the state of the diabetic carbohydrate metabolism or control, many of them believe that a blood sugar level above that of a normal person, 80-120 mg., is harmful. Perhaps this idea is better expressed in a conversation I overheard one morning between an interne and a diabetic. The patient was a female, aged 50 years, whose newly discovered diabetes of 10 days duration had been treated by diet and 20 units of globin insulin daily immediately after breakfast. She visited the interne in the clinic after having been submitted to venous blood examination for sugar content in the laboratory. While the interne was waiting for the blood sugar report he proceeded to question the patient concerning her general physical condition.

"Well, Mrs. Jones, how do you feel?"

"Doctor, I feel good. I sleep well and have no thirst. What a difference in feeling! I have also gained 2 lbs. in 3 days."

"That is very good, Mrs. Jones."

But when the doctor observed the blood sugar report of 240 mg. (2 hours after her breakfast and insulin) the expression upon his face changed.

"What is the matter doctor?" inquired the perplexed patient who had observed the facial change.

"Why, Mrs. Jones, you cannot be feeling so well, because your blood sugar level is elevated to 240 mg."

"Doctor," replied the excited patient, "What shall I do?" . . . .

What is the answer to "what shall the patient do?" since this type of conversation is not uncommon among internes, as well as among the practitioners.

Is a post-prandial blood sugar level of 240 mg. with insulin in a patient who is devoid of symptoms of diabetes, as well as of those symptoms associated with the general physical condition or disorders which are influenced by disturbed carbohydrate metabolism, harmful?

CLINICIANS' OBSERVATIONS

Anderson (7) claims "that even though hyperglycemia per se has never been proved directly to cause a single one of the more grave complications of the disease, glycemia is the only real yardstick to measure the adequacy of the control of the disease." He is of the opinion that persistent hyperglycemia is destructive of the "end organ" in carbohydrate metabolism. "Failing to recognize this principle the person surrenders himself to the very pathology in which it has been his challenge to correct and . . . he has however sacrificed every vestige of potential improvement in the patient's own intrinsic insulin mechanism, he has often converted his patient into an irreversible diabetic with heavy and increasing insulin needs."

Handelsman (8) claims that the maintenance of a urine sugar free and of a normal blood sugar serves two purposes—"(1) it insures 'rest' for the pancreas, inasmuch as hyperglycemia is known to stimulate the pancreas to secrete insulin and (2) it is an indication that other factors which have been excessively demanding insulin are under control." In his summary as to the prevention of arteriosclerosis he sums up the situation by advising withholding opinion until the cause, or causes, of arteriosclerosis are known. Paullin (9) emphasizes the necessity of maintaining a fasting blood sugar between 80 and 100 mg. per cent and 140-150 mg. per cent one hour after the carbohydrate meal. If the blood sugar level should reach 190-250 mg. or more mg. per cent two or more hours, after a large carbohydrate meal, the body, according to Paullin, is evidently unable to dispose normally of the ingested carbohydrate. Ricketts (10), speaking of the harmful effects of hyperglycemia, claims that evidence in animals indicates that both functional and structural injury to the Beta Cells may result, . . . "certainly during the incipient stages of diabetes and possibly even after the disease has become fixed. The evidence in man, while not so definitive, points in the same direction." He quotes various laboratory investigators whose work, based upon animal studies, reveals that pancreatic diabetes may give rise to degenerative lesions. In evaluating the laboratory observations he states that the situation with regard to the diabetic patient is still very confusing, since degenerative lesions are seen in mild, as well as in severe, di-

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abetes, controlled, as well as uncontrolled. He feels that the only common denominator predisposing to these complications is the duration of the disease. In his conclusion he feels that the lax control of the disease in both animals and man may be responsible for the degenerative complications and advises normaglycemia as the goal in the treatment of diabetic patients.

Boyd and his associates (11) have concluded from their studies of diabetic children, "that adequately controlled diabetes mellitus does not predispose the child to degenerative disease or to disturbances of growth." They are of the belief that, "the effects of poor control of diabetes are cumulative and terminate in serious complications or sequelae which lead to impaired function or to death." They claim "that impaired handling of sugar in the diabetic subject leads to certain perversions of the composition of body fluids, only one of which is the elevation of the level of dextrose in the blood and resultant glycosuria. A physiological level of control is one which would avoid any degree of hyperglycemia, hypoglycemia, or glycosuria and which would conserve the sugar handling function in maximal degree." Beaser (12) is of the opinion that in order to prevent progression of severity of diabetic complications one must detect and treat the earliest hyperglycemia or glycosuric stages of the disease. John (13) is of the opinion that "hyperglycemia has a deleterious effect on a diabetic state which thus becomes progressive resulting in a more severe diabetic state. He claims that extensive daily blood sugar studies are necessary to enable one properly to control any diabetic condition by distributing the insulin dosage wisely and adequately. Anderson (14) believes islet tissue may be protected by preventing sustained hyperglycemia. This can be accomplished by diet regulation alone, or combined with insulin. He apparently condemns "free diet" for juvenile diabetics, especially if they require less than 40 units of insulin daily, presuming that they still have functioning islet tissue because free diet will bring about a complete irreversibility of the diabetic state.

An editorial (15) survey of the management of the diabetic patient, claims the ideal is to keep the urine sugar-free. If 10 grams or less of sugar is excreted in each 24 hours, control of the diabetes is to be considered satisfactory. It also claims the excretion of sugar in the urine in 24 hours may reach 70 grams with normal blood sugar levels during the day. In the conditions of large amounts of urine sugar excretion according to the editorial the renal threshold must be considered as lowered, and the blood sugar level must be the sole criterion in evaluating the diabetic condition.

Mann and his associates (16) are apparently of the opinion that control of diabetes plays a role in arteriosclerosis when they state, . . . "there is no known young patient with comparable severe diabetes who has escaped arteriosclerotic complications while maintaining poor control of his disease." Marble (17) emphasizes that prolonged continuous hyperglycemia is harmful and claims that poor control of diabetes is the general factor apparently responsible for premature arteriosclerosis. Weinstein (18) claims that hyperglycemia per se may be harmful. Root (19) claims that the loss of control of the diabetes is the chief etiological factor of death from arteriosclerotic disease among those patients who have lived more than 15 years with diabetes.

Based upon their experience, Wilson and his associates (20) are of the belief that the factor in reducing the incidence and severity of degenerative complications is "continuous, aggressive treatment directed toward maintaining physiologic conditions, including normal levels of blood sugar."

Sherrill (21) believes that retinal changes can be retarded in diabetes when treatment avoids glycosuria and hyperglycemia as consistently as possible during each 24 hour period. He regards hyperglycemia as harmful. He is of the opinion that progression of ocular vascular lesions in diabetes is stimulated by conditions which accompany uncontrolled diabetes.

Peck (22) speaks of the great contribution of protamine zinc insulin when he emphasizes the protection of the patient from the ravage of uncontrolled active diabetes during the night. He places great reliance upon the blood and urine sugar tests as criteria of control, by maintaining them within reasonably normal limits.

Millard and Root's (23) conclusion of the effect of different types of treatment following a survey of the relationship between degenerative vascular lesions and diabetes mellitus in 110 autopsies of diabetic patients caused them to conclude that in their present series—"no cases are found in whom periods of carefully controlled diabetes were associated with the development of premature vascular disease in young people. In middle aged and older patients, in whom mild diabetes had long been controlled by dietary treatment, severe vascular lesions seemed to be postponed."

LABORATORY INVESTIGATION

The belief of these physicians, or clinical investigators, concerning the "harmfulness" of hyperglycemia is apparently based upon the laboratory results of various workers who were able to induce changes in the Beta cells of the Islets of Langerhans of the pancreas, through extra-pancreatic factors and bring about disturbances in the carbohydrate metabolism. Apparently the laboratory workers have conveyed the belief to the clinician that there exists a correlation between the degree of Islet damage and disturbance in the carbohydrate metabolism. Woerner (24) observed an extensive increase in Islet tissue from prolonged intravenous injections of dextrose in the guinea pig, which was especially marked in one partially depancreatized animal. Best and his co-workers (25) observed a decrease in the insulin content of the pancreas of rats during fasting, or when they were fed fat. However, when a balanced ration was given, they noted a restoration of insulin content. Haist and Best (26) have subsequently suggested, as a result of their studies in rats, that the Beta cells of the Islets are "rested" by fat feeding, fasting and insulin administration. Luken's and Dohan's (27) studies of the mechanism of the production and reversal of Islet cell damage caused them to advance the hypothesis that the blood glucose level may be a paramount factor in the pathogenesis and in the recovery of hydropic cells.

This inference was based upon the production of pancreatic lesions by partial pancreatectomy or pituitary extract, only when associated with hyperglycemia. Recovery of the islands according to these investigators, is coincident with the return of the blood sugar to normal levels, prior to irreversible damage to the Islands whether this is accomplished by insulin, dietary treatment or phlorhizin. Thus they are of the opinion, "that the level of the blood glucose is not only an index of the regulation of the carbohydrate metabolism, but also that it has directly or indirectly an influence upon the islands of Langerhans. This influence is pathogenic when the blood sugar is high and beneficial when hyperglycemia is controlled, provided the lesions are irreversible." Dohan and Luken's (28) more recent experimental studies on thirty-five cats, given 1 to 3 intraperitoneal injections of 20% glucose in 0.9% sodium chloride solution per day, revealed that 10 of these developed hydropic degeneration of the Islands of Langerhans, and, of this group, 3 exhibited persistent diabetes after the administration of glucose was discontinued. Twenty-five cats, however, failed to develop hydropic degeneration of the Islands of Langerhans. From these laboratory studies, they concluded that the development of the lesions was related not only to the degree, but, particularly, to the duration of the hyperglycemia, and that neither excessive caloric intake nor gain in weight appeared to be responsible. Harron and State (29) observed degranulation of the Islets of Langerhans when a group of dogs were given dextrose, 425 to 2,250 grams intravenously daily for as long as 9 days. They noted an initial transitory rise in blood sugar level followed by a latent period of normoglycemia for 3-7 days when sustained hyperglycemia developed. They concluded from their studies that these changes were indicative of functional overstrain or "exhaustion" of the B-cells, the site related to the production of insulin.

METHODS OF DIABETES CONTROL

Apparently, a review of the literature, as well as of the observations of various clinics throughout the world treating diabetics, reveals that many clinicians or investigators are in agreement that hyperglycemia may be harmful, as well as a responsible factor in the etiology of vascular degeneration.

Since the physicians or clinicians define the term hyperglycemia as that level of the blood sugar above 120 mg. per 100 c.c. of whole blood, it becomes apparent that a higher blood sugar level is abnormal and indicative of a disturbance in the carbohydrate metabolism. For these reasons most clinicians, in attempting to stabilize a person with diabetes, try to attain a blood sugar level equivalent to that of a normal or non-diabetic's level with the hope of avoiding or decelerating the progress of vascular degeneration, thereby helping to reduce the increasing incidence of associated vascular degenerations or "complications" in diabetes.

Since we have observed numerous patients whose diabetic conditions was discovered only by an associated vascular disease as retinitis, or cataract, or following an attack of coronary thrombosis, or beginning gangrene in one of the toes, or even in the foot, with only a moderate degree of hyperglycemia and no apparent diabetic symptoms such as increased thirst, urinary output or weight loss, we pondered as to their relationship to hyperglycemia. We noted that many of them prior to the discovery of diabetes, were able to carry on their normal physical and occupational duties.

We also observed that patients with known diabetes of many years duration, requiring large daily doses of insulin with high blood sugar levels, revealed no apparent evidence or symptoms of premature vascular degeneration by our present day method of examination.

At present there exist three schools of thought for "stabilizing or controlling diabetes, first, that school which depends solely upon the laboratory examination of the blood and urine for sugar as criteria of control. They believe that the peak of the normal or non-diabetic fasting blood sugar level of 120 mg. is the level most desirable for the diabetic. They are also of the opinion that a diabetic should be taught to examine his own urine for sugar content daily—at least 2 to 4 times a day—with the thought imbedded in his mind by his physician that a sugar-free urine is an index of "accurate" diabetic control and will help to delay, decelerate or prevent the progress of premature vascular degeneration. More recently, however, even in this school there appears to be a change of view concerning glycosuria. Many physicians are now of the opinion, which they are conveying to their patients, especially to those who are upon insulin therapy, that a trace of sugar in the urine is advisable and safer, because it is generally indicative of a slight hyperglycemia, a desirable level against insulin hypoglycemia reactions. This laboratory school of thought of "stabilizing" or "controlling" the patient with diabetes is apparently shared by many physicians.

The second school of thought or the "clinical" method of diabetic control is advanced by Tolstoi (30). He disagrees with the laboratory method of diabetic control, as advocated by a majority of the clinicians. He apparently—"disregards a hyperglycemia and glycosuria in the patient treated with protamine insulin, provided he is symptom free, ketone free and maintaining his weight. . . . Since no conclusive evidence has been found associating hyperglycemia and glycosuria with the development of hypertension, albuminuria or retinopathy, and since, furthermore, their deleterious effect upon insular function has not been substantiated clinically, the objections to the clinical technic are purely theoretical." He disregards the laboratory and concentrates upon the physical signs and symptoms of diabetes for guidance. In his 5 year survey of diabetics under his method of control he found that the incidence of vascular degeneration was not increased, as was thought by the "laboratory school." He concludes that hyperglycemia has not been proved to be an etiological factor in premature arteriosclerosis in diabetes. He is of the opinion that the assumption that vascular degenerative diseases are attributable to hyperglycemia is inferential and inconclusive. He claims (31) his method of control of diabetes is simple, safe and effective and that it has not pre-disposed the diabetic to an increased incidence of vascular degeneration. He apparently believes frequent laboratory examinations are not necessary for guidance of diabetic therapy.

THE COMPATIBLE SCHOOL OF HYPERGLYCEMIA CONTROL

The third or the modern school of controlling diabetes is one that is advocated by the present writers. It is known as the "Compatible School."

The questions that have been asked of the followers of the compatible school are:

I. "What is compatible hyperglycemia?"

II. "Can compatible post-prandial hyperglycemia bring about an improved state of carbohydrate metabolism, as evidenced by a lowering of the blood sugar, a decrease of insulin dosage, or even discontinuation of insulin therapy?"

In the "Compatible School" of guidance for our diabetic therapy we do not ignore the laboratory's findings, nor the patient's symptoms and signs of diabetes, nor those symptoms referable to other conditions or disorders associated with, or indirectly affected by, hyperglycemia. We do not depend upon the laboratory and entirely ignore the clinical or physical conditions of the patient. We combine both methods to help stabilize the diabetes. We therefore believe that both laboratory and clinical evidence are essential for adequate guidance in the control of diabetes.

(a) Post-Prandial Blood Sugar Level (1-6).

It became apparent from the summary and interpretation of our previous observations upon blood sugar levels, that in the normal and in the medical patients (non-diabetic), the blood sugar levels after a high carbohydrate meal, (a typical breakfast consisting of 1 cup of orange juice, ½ cup cornflakes, ¼ cup of cream, 2 tsp. of sugar, 2 scrambled eggs, 3 strips of bacon, 2 pats of butter, 2 slices of bread and 2 tsp. of sugar in a cup of coffee, containing 32 grams of protein, 64 grams of fat, 95.6 grams of carbohydrate), at 30 to 60 minute intervals for 3 hours compared with the fasting levels, revealed little change, whereas in the diabetic, there was marked elevation of the blood sugar 1 to 3 hours after this meal.

Thus, in stabilizing our patients with diabetes, (diet, insulin, etc.) we aim to bring the post-prandial blood sugar (1 to 3 hours, generally 2 hours after meals) to the level most compatible with the total well-being of the individual patient. It is that blood sugar level at which the patient has optimum physical comfort and is at the same time consistent with the condition of his cardiovascular system and other existing complications, age, insulin dose, occupation and physical activities. We observed that many patients, who were free from the usual diabetic symptoms or signs, but were subject to a variable degree of glycosuria, felt better mentally and physically when we reduced their post-prandial hyperglycemia to a lower level. A post-prandial blood sugar of 170-220 mg. per 100 c.c. with insulin was found to be the most compatible level. This level, however, is subject to individual variation depending upon the above factors. Without the aid of insulin, however, the compatible postprandial blood sugar may be lower, even 100 mg. or less.

It becomes evident in many instances that, in spite of the absence of diabetic symptoms with an elevated blood sugar level, there was a general physical improvement when the blood sugar was reduced to the compatible level. A still lower blood sugar level with insulin often causes physical discomfort.

It is not uncommon to observe a patient, whose diabetes was controlled by diet and insulin, complain of shortness of breath, weakness, uncomfortable sensation across the chest with a post-prandial blood sugar level of 220 mg.-240 mg., to be free from such distressing symptoms as well as from those of diabetes and general conditions associated with, or indirectly affected by, hyperglycemia when the blood sugar level was increased to 260 mg.-280 mg. (5).

In one of our studies, we made a careful individual analysis of our private patients to determine whether compatible hyperglycemia can bring about an improved carbohydrate metabolism, as evidenced by a lowered blood sugar and a decrease in, or a discontinuance of, insulin dose. We also made an observation of the relation of blood sugar level, insulin dose and duration of diabetes to arterio-vascular degeneration.

CLINICAL OBSERVATION

I. Using compatible hyperglycemia as a criterion of control, in our first group of 100 patients under our personal care, we observed that 53 of them were able to discontinue insulin. Of these 53, 34 were females and 19 males.

II. These patients ranged in age from 34 years to 80 years with the general average age of 63 years.

III. The apparent average duration of the diabetes prior to our therapy for the group was 2 years and 8 months. The duration period for the individual patient varied from 2 days to 18 years.

IV. The therapy prior to our own revealed that:

27 patients were upon diet;

23 patients were upon insulin;

3 patients were upon no special therapy.

V. It was also observed that the initial average blood sugar level of the 27 patients who were upon diet had been 239 mg., whereas for the 23 patients who had been upon insulin therapy it had been 209 mg. The three patients who were upon no special therapy had an average blood sugar level of 214 mg.

VI. The diet, prior to our diet therapy, revealed that the patients in the insulin and diet groups apparently did not adhere closely to their prescribed diets. None of these patients accurately estimated their food either by weight or by the common household methods. Many of them ate extra foods, especially rich in carbohydrates, such as pastry and candy. Others would miss one meal and eat more at the following meal, substituting "sweets" for the meal they omitted. Many of the patients were upon inadequate diets and none adhered closely to any special diets. Similar observations upon the diet habits of diabetes were previously reported by one of us (32).

VII. In the insulin group (23) the average insulin

dose upon their initial visit was 28 units varying from 10 to 80 units for the individual patient.

VIII. Symptomatology of both groups upon initial visit:

It was of interest to note some of the signs and symptoms related to us by the patients upon their initial visits and the apparent vascular disorders associated with them. Thus:

Pruritus, general and local, and weight loss were common. In some patients, loss of weight appeared to have had adverse mental effects. Increased thirst (over 10 glasses of fluid daily) and urination were frequent complaints, as well as impairment of vision, from mild to marked. Other complaints such as dyspnea upon physical exertion; swollen ankles and legs; productive and non-productive cough; general weakness; ulcer (diabetic) of toe and foot; "cramps" in calf muscles and toes during sleep or upon distant walking; numbness and tingling sensations in the extremities; mental depressions; headaches; forgetfulness; feeling of languor, "no pep;" "acid-stomach;" attacks of diarrhea or constipation; dry skin; weak spells; "hot flashes;" tremor; loss of appetite, and tightness across the chest when walking distances or following exertion appeared to be not uncommon.

It was also evident that none of the patients with the exception of three, was entirely symptom-free as related to diabetes or to the cardio-vascular, gastro-intestinal or neurological systems.

Since we were primarily interested in the circulatory system we tried to classify and enumerate the instances of arterial vascular disorders associated with their symptomatology as they occurred in the two groups—insulin and diet: Thus:

Complications or Associated Disorders	Insulin pts. (No. of instances)	Diet pts. (No. of instances)
Retinopathy	5	1
Cataracts	3	1
Cardiac Disease	3	2
Coronary artery disease	4	4
Hypertension	5	11
Peripheral arterial vascular disease	2	2
Foot ulcer	1	2

Thus we observed an equal number (23) of associated vascular disorders in each group—insulin and diet—upon the initial visit. Retinopathy and cataract were observed to be more prevalent in the insulin group, whereas coronary artery as well as peripheral vascular diseases were of equal occurrence. Hypertension was more prevalent in the diet group (11) as compared with the insulin group (5). None was observed in the 3 patients who were upon no special therapy.

OUR THERAPY FOR THE 53 PATIENTS

1. The condition of the patients (53), as evidenced by their general average blood sugar level of 220 mg., with symptoms and signs of uncontrolled diabetes, as well as symptoms associated with arterial vascular disorders, required insulin therapy, plain or globin insulin with zinc or both. The required average insulin dose for the group was 20 units a day. It varied however from 10 to 70 units for the individual patient.

(a) The average insulin period for the group was 4 months and 20 days. It varied from 2 days to 3 years and 5 months for the individual patient.

(b) The average post-prandial blood sugar level for the group (53 pts.) during the insulin period of our therapy was 162 mg., 58 mg. less than the initial general average level of 220 mg., whereas for the individual patient it varied from 104 mg. to 220 mg.

(c) Weight changes during our insulin therapy period as compared with the initial weight revealed:

17 patients had an average weight gain of 4.4 lbs.

29 patients had an average weight loss of 6.6 lbs.

7 patients had no weight change.

Thus we note that more patients lost weight (29) than gained weight (17).

2. After the above insulin period—average 4 months and 20 days— there occurred, with the general reduction of the average blood sugar level to 162 mg., an absence of the diabetic's symptoms and signs, as well as a marked reduction of those symptoms related to their associated disorders or physical condition. These changes or improvements made it possible to discontinue insulin therapy gradually.

The present non-insulin period (discontinuance of insulin) has existed for an average period of 2 years and 8 months. This latter period (non-insulin) varied for the individual patient from 2 months to 9 years and 6 months.

(a) The average post-prandial blood sugar level for the group (53 pts.) during the past non-insulin period was 141 mg., a reduction of 21 mg. as compared with the general average of 162 mg. as occurred during the insulin period. For the individual patient it varied from 101 to 191 mg. A reduction of 3 to 29 mg. difference when compared with the insulin period blood sugar levels of 104 to 220 mg.

(b) Weight changes during the diet or non-insulin period revealed that:

30 patients had an average weight gain of 9 pounds;

19 patients had an average weight loss of 7.4 pounds;

4 patients revealed no weight changes.

Summarizing our studies of weight changes in the 53 patients, we note that the average period of 2 years and 8 months for our diet therapy was longer than our insulin therapy period of 4 months and 20 days.

During this longer (diet) period we observed that more patients (30) upon diet therapy had a higher average weight gain, 9 lbs., than fewer patients (17) upon insulin therapy for a shorter period, 4.4 lbs.

The diet therapy also revealed the patients as having lower average blood sugar levels than during insulin therapy.

TABLE I

53 PATIENTS (GROUP-DISCONTINUED INSULIN)

Age in Years		Prior Duration of Diabetes		Initial Blood Sugar Level (Av.)			Insulin Patients (23) Dose on Visit	
General (Av.)	Individual (Var.)	Gen. (Av.)	Ind. (Var.)	Insulin (23 pts.)	Diet (27 pts.)	No Therapy (3 pts.)	Av.	Ind.
63 Yrs.	34 to 80 yrs.	2 yrs. and 8 mos.	2 days to 18 yrs.	209 mg.	239 mg.	214 mg.	28 units	10 to 80 units

Results of Our Therapy										
No. of pts.	Insulin Duration of Initial Therapy	Insulin Dose		Diet (Av.) Duration	Weight Changes (lbs.)			Blood Sugar Level		
		Gen. (Av.)	Ind. (Var.)		Loss	Gain	None	Gen.	Ind.
17	4 mos. and 20 days (Av.)	20 units	10 to 70 units			4.4		162 mg.	104 to 220 mg.
29					6.6				
7							None		
30						9		141 mg.	101 to 191 mg.
19			None	2 yrs. and 8 mos. (Av.)	7.4				
4							None		

Since the diet prescribed was liberal and adequately balanced and nearer to that of the normal person's high carbohydrate and protein, low fat diet, the patients apparently adhered to it more closely. This was evident in the result of our therapy when we observed an absence of diabetic symptoms as well as a decrease of those referable to the vascular system. This latter change was evidenced by the decrease of such symptoms as "leg-cramps" or numbness and less fatigue or "tired" legs, especially upon walking. The patients appeared to have a better attitude toward life and were mentally more alert. Dyspnea was less, especially dyspnea upon exertion. Improved vision in some patients was noted, with no change in others. The improvement was also evident in the three foot ulcers, which healed following toe amputation in one foot, 3 toes in another foot and antibiotic and other local non-surgical therapy in the third, thereby avoiding foot or leg amputation in all three instances.

OFF AND ON INSULIN GROUP (47 pts)

In the remaining 47 patients (24 females and 23 males) of the group of 100, we observed a general average age of 52 years, ranging from 21 to 82 years.

(a) The duration of therapy prior to our own revealed that

23 patients had been on insulin therapy for an average period of 4 years, ranging from 3 weeks to 15 years for the individual patient.

24 patients had been on diet therapy for an average period of 2 years and 7 months; ranging from 3 days to 30 years for the individual patient.

(b) The symptoms and signs, as related by the patients, were generally similar to those of the original group of 53 patients.

The vascular disorders apparently associated with their symptomatology in both groups were as follows:

Type of complications or associated disease	Insulin Group (no. of instances)	Diet Group (no. of instances)
Cataracts	3	1
Hypertension	4	4
Retinopathy	4	2
Coronary artery disease	3	2
Cardiac disease	4	3
Peripheral arterial vascular	6	6
Hemiplegia	1	1

Thus, prior to our therapy, we observed greater instances of arteriovascular disease in the insulin group, as noted by the 25 separate associated vascular disorders in 23 patients, than the 19 instances in 24 patients upon diet. Retinopathy and cataract appeared to predominate in the insulin group when compared with the diet group.

A similar occurrence of associated disorders was noted with the group of 53 patients who had discontinued insulin. Coronary artery disease was more frequent in the above insulin group of patients than in the diet group, whereas with the group of 53 patients who discontinued insulin it was of equal occurrence. Hypertension, and peripheral arterial vascular diseases were of equal occurrence in both groups of 47 patients, while in the group of 53 patients, hypertension was more prevalent in the diet group.

Upon the initial visit of the 23 patients in the insulin group the average blood sugar level was 220 mg., an increase of 12 mg. when compared with the insulin group in 53 patients; whereas for the diet (24 patients) group in the 47 patients the average blood sugar level was 210 mg., 29 mg. less than the 239 mg. observed in diet group of 53 patients.

TABLE II

INITIAL BLOOD SUGAR LEVELS (AV.)

(FIRST GROUP OF 100 PTS.)

47 Patients On and Off Insulin Group		53 Patients Discontinued Insulin Group		
Insulin (23 pts.)	Diet (24 pts.)	Insulin (23 pts.)	Diet (27 pts.)	No Therapy (3 pts.)
220 mg.	210 mg.	209 mg.	239 mg.	214 mg.

OUR THERAPY

In the group of 47 of the remaining 100 patients we were able to discontinue insulin and continue on diet therapy alone for a short period. Because of the elevation of the average blood sugar level to 242 mg. in 24 patients of this group of 47 and suspicious or vague symptoms of diabetes, as well as of symptoms referable to the general physical condition, i.e., those symptoms which were affected by or associated with the hyperglycemia such as general or leg weakness, impaired appetite, and mental depression, we placed the 24 diet patients upon insulin as the initial therapy. The average duration period on insulin therapy was 5 months. This insulin period varied for the individual patient from 3 weeks to 2 years. The average insulin dose for the group was 14 units, ranging from 10 to 28 units per day for the individual patient.

(a) The general average post-prandial blood sugar level during the insulin period was 171 mg., ranging from 135 to 240 mg. for the individual patient.

(b) Because of the gradual reduction of the blood sugar level, as evidenced by the occurrence of mild insulin hypoglycemia reactions and the absence of those symptoms which are usually associated with hyperglycemia, insulin was discontinued in this group for an average period of 9 months.

During this diet period the post-prandial blood sugar was reduced to the average level of 144 mg., 27 mg. less than the level during the insulin therapy period.

(c) Following this period there occurred a moderate increase in the blood sugar level—average of 240 mg., but with no evidence of diabetic symptoms. There was, however, an increase of those symptoms referable to the general physical condition, such as tiredness, "no pep," easy fatigability following physical exertion, but there was no increased thirst, urination or weight loss. In some patients of the group appetite was diminished, whereas in others it was increased, and in still others there was no change. Since these symptoms did not exist with lower blood sugar levels, we felt the signs or symptoms, though not the usual diabetic ones, were associated with hyperglycemia sufficiently to warrant insulin therapy. The average daily insulin dose was 18 units, varying from 16 to 32 units per day for the individual patient. This latter insulin therapy was maintained for an average period of 13 months; varying from 2 months to 3 years for the individual patient.

The remaining 23 of the 47 patients we placed upon diet therapy, because the average blood sugar level was 220 mg., ranging from 100 to 230 mg. for the individual patient and because of the absence of diabetic as well as physical (non-diabetic) symptoms, which are infrequently associated with hyperglycemia. With the reduction of the average blood sugar level to 152 mg. upon the diet therapy (ranging from 100 to 209 mg. for the individual patient), we did observe a physical improvement as well as a sense of well being which was not evident prior to our diet therapy.

(a) The diet therapy period averaged 2 years, ranging from 4 weeks to 7 years and 9 months for the individual patient.

(b) After the diet period in this latter group of 23 patients, we noted that with the general average increase in the blood sugar level to 248 mg., mild symptoms of diabetes became evident. These included a slight increase in thirst, from the usual 3-4 glasses of water a day to 6-10, and increase in appetite, as well as an improvement in those symptoms referable to the general physical condition of the patient, such as weakness and tiredness in the lower extremities. Also, we noted no weight loss.

These symptoms and signs associated with the increased blood sugar level were apparently indications for insulin therapy, which we have maintained for the past average duration period of 1 year and 5 months. The average insulin dose was 19 units, varying from 12 to 32 units for the individual patient. The average post-prandial blood sugar level during the insulin therapy period was 208 mg., ranging from 168 to 248 mg. for the individual patient.

TABLE III

RESULTS OF OUR FIRST INSULIN THERAPY
(24 DIET PATIENTS OF 47)

Duration (Prior Period)		Blood Sugar Level (Initial) Prior to Insulin Therapy	Insulin Period (First)					
			Av. Dose		Duration (Av.)		Blood Sugar Level (Av.)	
Gen.	Ind.		Gen.	Ind.	Gen.	Ind.	Gen.	Ind.
2 yrs. and 7 mos.	3 days to 30 yrs.	242 mg. (Av.)	14 units	10 to 28 units	5 mos.	3 wks. to 2 yrs.	171 mg.	135 to 240 mg.

RESULTS OF OUR DIET THERAPY

Non-Insulin Period

Duration (Average)		Blood Sugar Level (Av.)	
General	Individual	General	Individual
9 Months	8 days to 3 years	144 mg.	100 to 152 mg.

SUMMARY OF 47 PATIENTS STUDIES

Thus in 47 patients, we observed that 24 of them were first given insulin therapy for an average period of 5 months, after which it was discontinued for 9 months. After the latter period there occurred in the group of patients an average increased blood sugar level as well as an increase in those symptoms related to hyperglycemia and impaired general physical condition. These changes were corrected when the patients were placed upon insulin for a second time and have

RESULTS OF OUR SECOND INSULIN THERAPY

Insulin Period (Second)					
Blood Sugar Level (Av.)		Insulin Dose (Av.)		Duration (Av.)	
General	Individual	Gen.	Ind.	Gen.	Ind.
240 mg.	138 to 258 mg.	18 units	16 to 32 units	13 mos.	2 mos. to 3 yrs.

TABLE IV

ON AND OFF INSULIN THERAPY GROUP
(23 INSULIN PATIENTS OF 47)

Duration (Prior) Insulin Therapy		Initial Blood Sugar Level (Av.)		Results of Our Diet Therapy			
				Diet Period (Non-Insulin)			
				Duration (Av.)		Blood Sugar Level (Av.)	
Gen.	Ind.	Gen.	Ind.	Gen.	Ind.	General	Individual
4 years	3 wks. to 15 yrs.	221 mg.	100 to 260 mg.	2 years	4 wks. to 7 yrs. and 9 mos.	152 mg.	100 to 209 mg.

RESULTS OF OUR INSULIN THERAPY

Initial Blood Sugar Level (Av.)		Insulin Period					
		Dose (Av.)		Duration (Av.)		Blood mg. (Av.)	
Gen.	Ind.	Gen.	Ind.	Gen.	Ind.	Gen.	Ind.
248 mg.	160 to 259 mg.	19 units	12 to 32 units	1 year and 5 mos.	4 mos. to 3 yrs.	208 mg.	168 to 248 mg.

remained corrected for the past 13 months. The average insulin dose during this second period was 18 units a day, an increase of 4 units, as compared with the first period of insulin therapy of 14 units a day.

In the remaining 23 patients, diet therapy was first prescribed because the initial average post-prandial blood sugar level of 220 mg. was not associated with symptoms of diabetes nor with those symptoms referable to the general physical condition which might be influenced by the disturbed carbohydrate metabolism. The diet therapy was maintained for an average period of 2 years. During this latter period, however, we observed a reduction of the average post-prandial blood sugar level to 152 mg., as well as an improvement in the physical well-being of the patient.

Following this period there was an average increase in the blood sugar level to 248 mg., as well as an appearance of mild symptoms of diabetes and symptoms referable to the general physical condition such as increased fatigue following physical exertion, lack of real "pep." These latter changes became evident with the moderate increase in the blood sugar level. When insulin was administered the symptoms, though mild, disappeared. The patients felt stronger and mentally more alert. The insulin therapy was maintained for the past average period of 1 year and 5 months. During this period the average insulin dose was 19 units and the average post-prandial blood sugar level was 208 mg.

The present weights noted in the 47 patients, all of whom are upon insulin therapy, when compared with their weights at the time of their initial visits revealed little average weight change. In 22 patients there was an average weight gain of 5.9 lbs., 7.8 lbs. average weight loss in 22 other patients, and no weight changes in the remaining 3 patients.

CONCLUSION

I. Compatible method, a new mode of control, is advocated in helping to guide diabetic therapy because:

(a) 53% of our group of 100 patients discontinued insulin for an average period, which has existed for 2 years and 8 months. This latter period for the individual patient varied from 2 months to 9 years and 6 months.

(b) There was a greater incidence of weight gain (30 patients had an average gain of 9 lbs.) during the diet period (interval in which insulin was discon-

tinued) than during the initial insulin therapy period (17 patients with an average gain of 4.4 lbs.) in the 53 patients.

In the 47 patients who were on or off insulin therapy there was no significant comparable change in the weight loss and gain.

(c) It combines the clinical and the laboratory methods to help stabilize the diabetes.

II. Clinical evidence of arteriovascular degeneration in the various groups did not appear to be related to the level of the blood sugar, insulin therapy, or apparent duration of the diabetes.

Part II. a. Observation of a second series of 100 patients upon diet therapy alone.

b. Statistical analysis of the relationship of the age of the patient, daily dose of insulin, level of the blood sugar and apparent duration of the diabetes to premature arteriosclerosis or associated vascular disease.

"HARMFULNESS" OF HYPERGLYCEMIA

A review of the literature reveals that the most common of the two schools of thought among the physicians, as described in our previous studies for the control of diabetes mellitus, believes that hyperglycemia is harmful. The physicians of this latter school are of the opinion that the blood sugar

1. Is the only real measure of adequacy of diabetic control (7).

2. Above 80-120 mg. is harmful and that it may convert the patient into an irreversible diabetic with heavy and increasing insulin needs (7).

3. At a normal range "insures" rest for the pancreas and that other factors which have been demanding excessive insulin are under control (8).

4. Level maintained for 2 or more hours at 190-230 mg.% will make the body unable to dispose normally of the ingested carbohydrate (9).

5. Elevation or hyperglycemia per se is harmful (18), as evidenced by the functional and structural injury to the beta cells in laboratory animals (10), and that it is apparently a predisposing factor to degenerative lesions (10).

6. At a normal level should be the goal in the treatment of diabetes (10).

7. At a physiological level of control is a level which avoids hyperglycemia, hypoglycemia or glycosuria and that a deviation from this level of control may result in hyperglycemia with resultant glycosuria, indicative of poor control, the effects of which are cumulative, terminating in "serious complications or sequelae which lead to impaired function or to death" (11).

8. Elevation's (hyperglycemia level) earliest detection and prompt treatment will prevent progression of severity of diabetic complications (12).

9. Increase (hyperglycemia) has a deleterious effect, which is progressive, with a resultant severe diabetic state (13).

10. At a normal level or one that is void of sustained hyperglycemia may protect islet tissue (14).

11. Increase, or at a hyperglycemia level, over a prolonged period is harmful (17) and that poor control is a responsible factor in premature arteriosclerosis or death from arteriosclerotic disease among those patients who have lived more than 15 years with diabetes (19).

The aim or goal therefore of this school in diabetic therapy is to reduce the blood sugar level to that of a normal person, taking a fasting blood sugar level of 120 mg.% or less as a criterion of normalcy.

CLINICAL OBSERVATIONS

That we are in disagreement with the opinion that compatible postprandial hyperglycemia is harmful to the carbohydrate metabolism is evident from our previous studies of the first group of 100 patients. In this latter group we were able to discontinue insulin with compatible postprandial hyperglycemia in 53% of the patients for an average period of 2 years and 8 months, which ranged from 2 months to 9 years and 6 months for the individual patient.

In spite of these results we decided to maintain and observe a second selective group of 100 patients with a compatible postprandial blood sugar level whom we would maintain on diet alone.

Upon the initial visit of these 100 cases we made the following observations:

1. Age of patient varied from 24 to 75 years, average 55 years.

2. Apparent duration of diabetes prior to our therapy revealed a general average of 2 years and 8 days, with a variation for the individual patient from 3 days to 18 years.

3. Therapy prior to ours:

(a) 77 patients had been treated by diet.

(b) 20 patients had been treated with insulin.

(c) 3 patients had had no therapy (no specific diet or insulin).

4. The general symptoms observed upon the initial visit were similar to those of many diabetics. The symptoms generally observed with inadequately controlled diabetes, such as moderate increase in thirst and urination with a variable change in appetite, appeared to be slightly evident in a few patients. In some there was a slight increase, in others a decrease, with no change in the remaining group. No marked weight loss was noted.

There were, however, variable changes in general physical conditions. Some patients complained of weakness, loss of "pep" or a feeling of general "rundown" or slight debility. Many suffered from "nervousness" and complained of vague pains throughout the body.

5. The associated vascular disorders and compli-

cations of diabetes mellitus noted upon the initial visit (in both groups, insulin and diet) were as follows:

"Complications" or associated disorders	Patient taking insulin (total cases 20)	Patient on diet therapy alone (total cases 77)
Retinopathy	4	7
Hypertension	2	24
Cardiac	1	4
Peripheral vascular disease	6	14
Ulcer right large toe	3	0
Hemiplegia	0	2
Coronary artery disease	0	4
Cataract	0	4

Thus we observed 16 instances of associated arterial vascular disorders in 20 insulin patients, 59 in 77 diet patients on diet therapy alone, and none in the 3 patients who were upon no specific therapy. Diabetic ulcer of the foot was present in 3 instances among the insulin patients but was not observed among the patients on diet therapy, whereas the incidence of peripheral arterial vascular, coronary artery and cardiac disease was greater among the diet group.

6. The average 1-3 hour post-prandial blood sugar level (of both groups) upon the initial visit and as the result of our therapy was as follows:

I. 223 mg. in the patients (20) with a range from 148 to 330 mg. for the individual patient. After our treatment the average blood sugar level was 153 mg. ranging from 110 to 168 mg.

II. 221 mg. in the diet patients (77) with a range from 140 to 250 mg. for the individual patient. Following our therapy the average level was 176 mg., varying from 110 to 190 mg.

III. 170 mg. for the 3 patients who were upon no specific therapy, with a range from 100 to 200 mg., but following our therapy the average was 130 mg. with a range from 97 to 140 mg.

WEIGHT CHANGES

I. The insulin patients' (20) average weight upon initial visit was 156 lbs., but following our therapy the average weight was 159 lbs., a gain of 3 lbs.

II. The diet patients' (77) average weight was 153 lbs., but following our period of therapy was 163 lbs., a gain of 10 lbs.

III. The initial (average) weight for the 3 patients who were upon no specific therapy was 149 lbs., but following our therapy it was 152 lbs., an average gain of 3 lbs.

Thus the initial average blood sugar level for both groups—insulin and diet was 222 mg. During our therapy the average was reduced to 165 mg., an average difference of 57 mg.

The initial average weight for both groups was 152 lbs., but during our therapy for both groups it was increased to 158 lbs., an average gain of 6 lbs.

STATISTICAL ANALYSIS

Following these observations we decided to make a statistical analysis of the relationship of the age of the patient, daily dose of insulin, level of the blood sugar and apparent duration of the diabetes to premature arteriosclerosis or associated vascular disease.

We are aware that the term "generalized arteriosclerosis" as emphasized by Burchell and his associates (33), is accepted with reservation as they state —"from the degree of atherosclerosis in one part of the body as for instance the heart, one can not predict the degree of similar lesions in other parts of the body, as in the brain."

In our diabetics with associated vascular disorders or "complications" we considered the following criteria:

1. Hypertension (developing during period of observation):
   (1) Systolic blood pressure over 140.
   (2) Diastolic blood pressure 90 or over.

TABLE V

INITIAL OBSERVATIONS IN 100 Pts. (Prior to Our Therapy)

Average Age		Av. Duration of Diabetes		Blood Sugar Level (Av.) Insulin (20 pts.)		Diet (77 pts.)		No Therapy (3 pts.)		Weight (Average)		
General	Individual	Gen.	Ind.	Gen. (Av.	Ind. (Var.)	Gen.	Ind.	Gen.	Ind.	Insulin (20 pts.)	Diet (77pts.)	No Therapy (3 pts.)
55 yrs.	24 yrs. to 75 yrs.	2 yrs. and 8 days	3 days to 18 yrs.	223 mg.	148 mg. to 330 mg.	221 mg.	140 mg. to 250 mg.	170 mg.	100 mg. to 200 mg.	156 lbs.	153 lbs.	149 lbs.

RESULTS OF OUR THERAPY (DIET)

Duration of Therapy (Av.)		Blood Sugar Level (Av.) Insulin (20 pts.)		Diet (77 pts.)		3 Patients		Weight Changes (Av.) Insulin (20 pts.)	Diet (77 pts.)	3 pts.
Gen.	Ind	Gen.	Ind.	Gen.	Ind.	Gen.	Ind.	Gen.	Gen.	Gen.
2 yrs. and 9 mos.	3 wks. to 10 yrs.	153 mg.	100 to 168 mg.	176 mg.	110 to 190 mg.	130 mg.	97 to 140 mg.	159 lbs.	163 lbs.	152 lbs.

2. Coronary Artery Disease:
   (1) Anginal pain with EKG changes.
   (2) EKG evidence of recent or old infarction.
   (3) EKG evidence of myocardial damage in absence of hypertension.

3. Cardiac Disease (due to hypertension and/or coronary disease). Enlargement of heart and/or EKG evidence of cardiac disease.

4. Cataracts:
   Significant visual impairment.
   Includes Grade +++ (considerable visual disturbances; fundi poorly visible) and Grade ++++ (ready for surgery).

5. Retinopathy (Grade +++):
   With hemorrhages and exudates.

(1) Relationship between *age* and *complications in diabetes.*

Type of "Complications"	*Average Age*	*No. of Cases*
No significant complications	52.9	23
Two or more significant complications	63.1**	37
Hypertension	61.8**	32
Coronary Artery Disease	66.1**	29
Cardiac Disease	64.2	46
Cataracts	66.0**	16
Retinopathy	60.4*	34

(2) Relationship between known *duration* of diabetes and *complications in diabetes.*

Type of Complication	*Average Known Duration*
No significant complications	15.7 years
Two or more significant complications	16.7
Hypertension	15.8
Coronary Artery Disease	16.2
Cardiac Disease	15.5
Cataracts	16.5
Retinopathy	15.9

(3) Relationship between *percentage of blood sugars over 220 complications in diabetes.*

Types of Complication	*Average % B. S. over 220*
No significant complications	36.1%
Two or more significant complications	37.5%
Hypertension	38.5
Coronary Artery Disease	39.1
Cardiac Disease	38.1
Cataracts	34.4
Retinopathy	38.6

* Significant difference from average age of cases with no complications. t 1.96; p. 05.

** Highly significant difference from average age of cases with no complications. t.2.58; p. 01.

(The "T-test" was used to demonstrate significance of the differences between means.)

(4) Relationship between average *Insulin dose* and *complications in diabetes.*

Type of Complications	*Average Insulin Dose*
No significant complications	35.0
Two or more significant complications	40.8
Hypertension	39.6
Coronary Artery Disease	37.1
Cardiac Disease	38.4
Cataracts	31.9
Retinopathy	39.9

(None of the above differences were found to be statistically significant, as measured by the "t-test.")

(5) Relationship between the *number of years on Insulin* and *complications in diabetes.*

Type of Complication	*Average No. of years on Insulin*
No significant complications	12.2
Two or more significant complications	13.4
Hypertension	12.7
Coronary Artery Disease	12.3
Cardiac Disease	12.3
Cataracts	13.5
Retinopathy	13.1

(None of the above differences were found to be statistically significant, as measured by the "t-test.")

(6) Differences between diabetic patients 45 years of age and over with no significant complications, or with two or more significant complications.

Diabetic Patients 45 Years of Age and Over

	No Significant Complications	*2 or More Significant Complications*
Age	59.7	63.1
Known Duration	16.0	16.7
% Sugars over 220	32.8	37.5
Insulin Dose	30.0	40.8
Years on Insulin	11.7	13.4

(None of the above differences were found to be statistically significant, as measured by the "t-test.")

To further clarify our clinical studies into the relationship of hyperglycemia to vascular degeneration we studied a group of 45 patients with age range from 44 to 77 years who have had leg amputations. The observations revealed the average daily insulin dose to be 29 units, and the average fasting and 2 hour postprandial blood sugar levels to be 152 mg. and 185 mg. respectively. (Table 6)

TABLE VI

LEG AMPUTATIONS (GANGRENE)

No. of pts.	Age Variations	Insulin Dose (Av.)	Blood Sugar Level (Av.)	
			Fast	2 hrs. Post Prandial
45	44 yrs. to 77 yrs.	29 units	152 mg.	185 mg.

Forty-four patients with age ranging from 15 to 72 years and with average duration of diabetes of 8 years ranging from 1 to 20 years failed to reveal arteriosclerotic degeneration by our present day methods of examination. The daily insulin dose for this group varied from 52 to 270 units. Fourteen patients of this group have had diabetes 10 or more years. (Table 7).

TABLE VII

NO EVIDENCE OF PREMATURE ARTERIO-SCLEROSIS

No. of pts.	Age	Duration of Diabetes (Apparent)		Insulin Dose Ind. (Var.)	Comments
	Ind. (Var.)	Average	Ind. (Var.)		
44	15 to 72 yrs.	8 years	1 to 20 years	52 to 270 units	14 pts. of this group had Diabetes 10 or more years

A group of 100 patients, with ages varying from 17 to 69 years, revealed that 21 of these, with average duration of diabetes of 15 years failed to reveal vascular complications. Two or more significant vascular complications were observed in the remaining 79 cases, with an average duration of diabetes of 17 years.

RESULTS AND CONCLUSION

The results of our statistical and clinical survey revealed the following:

(1) That in the group of 100 patients the average weight gain under our diet therapy was 6 lbs.

(a) that an average weight increase of 3 lbs. was noted in our diet therapy in those 20 patients who had been previously treated by insulin and a 10 lb. average in those patients (77) who had been on diet.

(2) The apparent known duration of diabetes plays no role in the incidence of vascular complications (2), no relationship between blood sugar levels over 200 mg. and complications (3) and that there is no relationship between the average insulin dose and "vascular complications."

Part III. a. Interpretation of Our Observations.
b. Conclusion.

A review of the literature, as well as an observation of the various diabetic clinics throughout the world, reveals that there exists a school of thought among physicians postulating that a fasting blood sugar level above that of the normal (80-120 mg. per 100 c.c. of whole blood) is harmful in the diabetic, especially to the vascular system. This belief is so firmly embedded that many physicians are unequivocal in their advice to their patients. They insist that daily fractional urine examinations must be negative for sugar, and that the blood sugar level must be maintained at the normal or non-diabetic's level otherwise the patient may "slip" into the "valley of disaster"—vascular degeneration—which may bring about incurable blindness, coronary disease, or gangrene. As a consequence of this teaching it is not uncommon to observe patients become almost hysterical, when they observe sugar in their urine, or know that their blood sugar has been elevated to 180 mg. or more.

When on the other hand, the conscientious patient, who has apparently maintained a normal blood sugar level and a sugar free urine, develops some form of retinopathy or gangrene what explanation or answer can the physician give? Can he say positively that the duration of the diabetes was responsible? Does the physician know how long the diabetes has actually existed?

Is hyperglycemia a true index of the extent of the deranged carbohydrate metabolism?

This is a moot question because we believe blood sugar elevation is only one of multiple disturbances of metabolism in diabetes mellitus. Its detection, however, is the only known practical method which gives the physician the diagnosis and to a measurable degree an index to the progress of his treatment. If the height of the blood sugar is accepted as the sole determining factor in the diabetic patient's condition, then it is often misleading. This was realized when we had observed asymptomatic as well as symptomatic diabetes among patients with blood sugar of 190 mg.% or more. We have also noted symptoms of diabetes in patients with a blood sugar level of 250 mg., whereas at a higher level following treatment with insulin the symptoms were not evident.

It becomes apparent that either symptoms or laboratory results alone as criterion for the guidance of diabetic therapy are not always dependable. The combination of both, however, as advocated in the compatible school will give more information for better guidance in diabetic therapy.

Are there different etiological factors interfering with the insulin mechanism? A partial answer to the latter question is that experimental diabetes in animals may be brought about in several ways—removing the pancreas (27), giving alloxan (the ureide of mesoxalic acid), a specific toxin for the beta cells of the Islets of Langerhans (34, 35); injecting uric acid intra-peritoneally into rabbits with lowered blood glutathione caused by a diet deficient in methionine and cystine (36), administration of glucose intraperitoneally in cats (28), prolonged administration of glucose intravenously in dogs (29); injection of anterior pituitary extract in dogs (37) or cats (38). Apparently the laboratory results in animals do not always correlate with those in human diabetes, as evidenced by the absence of pathology in the islets or the beta cells of the pancreas at post-mortem in patients who have died of diabetes.

In our survey of associated vascular disorders or complications as classified above we observed (1) that the incidence of associated or "complicated" vascular disorders was independent of the apparent duration of diabetes (2) there existed no statistically significant relationship between blood sugar levels and complications or associated conditions (3), there was no statistically significant relationship between the average insulin dose and associated or complicating vascular disorders.

These latter conclusions are supported by another survey in which we observed 45 leg amputations because of gangrene in patients (Table No. 6) who have had an average fasting blood sugar level of 152 mg. and an average post-prandial level of 185 mg. and who were receiving an average daily insulin dose of 29 units. In another group of forty-four patients who were upon larger daily doses of insulin (52 to 270 units) with duration of diabetes varying from one to twenty years, there was no evidence of vascular complications or associated disorders.

It is not uncommon to observe a diabetic who had discontinued insulin for several months or years because of an apparently normal carbohydrate metabolism develop gangrene, retinopathy, coronary or vascular disease. Why such conditions have developed when the patient has adhered closely to instructions and the blood sugar has been at a normal level can not be answered with accuracy by our present day knowledge.

DIABETES CONTROL

Of the three schools of thought as previously described, we advocate the "compatible" school as safer for the patient. We are opposed to the belief that a postprandial blood sugar rise with insulin therapy to a level of 170-240 mg.% or slightly higher, depending upon the patient's diabetic symptomatology, age, the condition of the cardiovascular system, occupation, existing complications, in the absence of symptoms associated with hyperglycemia, will injure the diabetic's insulin mechanism, or induce, precipitate, or accelerate degeneration.

ARTERIOSCLEROSIS

Bell (39) states that the mechanism by which the diabetes accelerates atherosclerosis is unknown. The degree or extent of arterial disease in diabetes according to Bell is not related to the intensity or duration of diabetes. He has observed vascular disease to be just as severe in mild diabetics controlled by diet alone as in severe diabetics treated with large doses of insulin.

Ducas (40) believes that the main danger to diabetics who have escaped acidosis is the appearance of progressive vascular and sensory degenerative disorders. The conditions of their genesis being unknown, it is to be hoped, according to Ducas, that some day we may know these conditions better through a more thorough study, and thus be able to prevent their appearance.

Hedges (41) after autopsy studies of 32 patients with the diagnosis of diabetes, concluded that insulin therapy does not check the development of degenerative lesions, even though it may help control the hyperglycemia of diabetes.

Moschcowitz (42) is of the opinion, as based upon evidence submitted, that in older individuals hyperplastic arteriosclerosis precedes diabetes but does not follow it.

Barr and his associates' (43) studies of changes in protein and cholesterol distribution in conditions which are known to predispose to early and extensive atherosclerosis revealed apparent discrepancies in a number of diabetics. In some of the young patients, extreme abnormalities were apparent, while in others the changes were not very significant. From their present data they were not able to differentiate the diabetics with a tendency toward atherosclerosis from those without it. Using the criteria of their investigation they found that the diabetic group cannot be regarded as statistically homogenous. In many diabetics, changes in protein and cholesterol distribution were apparent before vascular complications of the disease were clinically recognizable. They conclude from their observations that future studies relating lipids of plasma to deposition of lipids in tissue must consider their combinations with protein. It is their belief that the pathogenesis of atherosclerosis can be better clarified and earlier recognized by a more thorough investigation of the protein lipid relationship.

Lukens (44) in his appraisal of diabetic therapy, admits that well treated patients may develop lesions of the heart or feet. He also states that exemption from these lesions cannot be promised to patients.

Davidson and his associates' (44) studies showed no correlation between the height of the blood glucose and the degree of peripheral vascular disease.

Dry and Hines (46) postulate the existence of a biologic background for the development of advanced arterio-clerosis in the presence of diabetes mellitus—"an inherent weakness or an abiotrophy exists which affects both insulin-producing tissues and the vascular system and which requires in each instance only an additional stimulus to bring about pathological changes—a stimulus such as obesity, an infectious illness, overfeeding, hypertension or hyperlipemia."

Ivy's (47) description of degenerative diseases—diabetes mellitus with arteriosclerosis, chronic myocarditis, chronic nephritis, cirrhosis of the liver and the pancreas, gout, otosclerosis and senile deafness, postmenopausal or senile osteoporosis—is that they are "the non-infectious and non-parasitic diseases which kill and maim aging persons prematurely and for which it is biologically rational to hope that the causes, the prevention and better management may be found." He names insulin in diabetes as one of the specific drugs as a substitute for function lost from degenerative disease, or from the natural involution of an organ.

Stearns and his associates (48) are in favor of mild hyperglycemia in preference to "knife-edge" control of the blood sugar in diabetic patients with severe coronary arteriosclerosis, in order to avoid the risk of precipitating myocardial infarction as a sequel to insulin hypoglycemia. Adlersberg and his associates (49) discuss the existence of the close relationship of atherosclerosis to familial xanthomatosis, an hereditary disorder. They believe that many factors other than an hereditary disturbance of cholesterol metabolism as evidenced by hypercholesterolemia are involved in the pathogenesis of atheroma. They claim an hereditary disturbance of lipid metabolism is only one of the conditioning factors for the development of coronary artery disease.

Kirk and his associates (50) observed no certain relationship between the serum cholesterol concentra-

tion and the clinically demonstrable incidence of medical arteriosclerosis in 118 persons between 45 and 96 years of age. From their studies they conclude that the thyroid has an influence upon the development of medial arteriosclerosis.

Katz and his associates (51) observed that diabetes increased the mortality rate in myocardial infarction in the first 2 months. 50.8 percent of the diabetics died in the first two months, compared with 26.6 percent of the non-diabetics. The over-all mortality rate was 68.3 percent among diabetics compared with 42.4 percent among non-diabetics. Thus, they are of the opinion that even though the presence of diabetes does not increase the mortality rate after 2 months, it apparently brought about an earlier death among those who did die. They conclude—"the ill effects of diabetes so far as death is concerned manifest themselves early in the period after infarction and that the later prognosis is no worse than for the group as a whole."

Bell's (52) post-mortem studies of vascular diseases as causes of death in diabetic individuals revealed 17% between 1910-22; 41.6% between 1922-33; and 49.6% between 1936-1948. Deaths in diabetics from hypoglycemia in the insulin era, were 0.4% from 1922-33 and had increased to 1.2% from 1936-1948.

In Bell's discussion of the relation of death from vascular disease to the duration of diabetes he claims the incidence of vascular disease increases with age in both diabetic and non-diabetic individuals. He is of the opinion that in adult diabetics the onset of the disease is often so indefinite that an accurate approximation of its duration cannot be made. He is also of the belief that the duration of diabetes has little or no effect upon the development of arteriosclerosis in those persons who die after the age of 60 years. The influence of diabetes was noted after 10 years, but it was more evident after 15 years duration of diabetes. Apparently this latter influence was not contributory as a cause of vascular death in over one-third of the individuals who survived 15 years or more of diabetes, even though vascular disease was present at the time of death. He concludes from these studies, "diabetes of long standing, therefore does not necessarily result in severe atherosclerosis." In this final conclusion, Bell claims the development of severe vascular lesions is independent of the severity of diabetes.

In their discussion of the etiology of atherosclerosis in diabetes, Warren and LeCompte (53) admit that there is no doubt that diabetics are prone to develop it at an earlier age and to a greater extent than other persons, but state that the causes of the condition are still obscure. They admit the question of the relationship of the degree of diabetic control to the incidence of vascular complications is a controversial one.

Lukens (54) in his discussion of the relation of hyperglycemia to complications says "it is clear that there are some aspects of diabetes and its complications in which hyperglycemia may be harmful. In other aspects of the disease, there is no evidence that hyperglycemia is injurious. It seems that experimental observations will add to the meager facts, but as yet they lead to no final conclusions on the role of hyperglycemia as a pathogen." He is of the opinion "that in most, if not all, conditions in which blood sugar is elevated there are many other concomitant abnormalities."

Pillow and Palmer (55) believe that in the majority of the diabetics a metabolic disorder may exist as an etiological factor in premature vascular disease which is not always an integral part of the primary disease. If the thought exists that premature vascular disease is the result of poorly controlled diabetes, it becomes difficult, according to them, to explain its absence in those patients whose diabetes has been poorly controlled after 15 years, as well as its existence with extensive vascular damage in other patients, whose diabetes is milder and of a shorter duration.

Zisserman (56), in his survey of a series of 155 deaths in patients with diabetes during the period 1930-1938, concludes that "it becomes more and more apparent that insulin therapy, despite its great value in the treatment of diabetes mellitus is by no means a panacea for the many complications seen in the course of this chronic disease." DeZoysa's (57) observations of 180 diabetics revealed that 5% suffered some degree of peripheral vascular occlusive disease. His explanation for the low incidence of vascular disease among diabetics in the tropical country of Ceylon was the native low fat diet with absence of hypercholesteremia and obesity.

King (58) mentions 3 main pathological lesions of diabetes—presence of glycogen in the liver cell nuclei and certain lesions in the glomeruli and in the papillae of the kidney. Even though they are found in non-diabetics he claims their presence is sufficient pathological evidence that the patient had suffered from diabetes.

Kountz and Chieff's (59) studies suggest some relationship between the onset of degeneration and a deceleration of the oxidative processes of the body. They are of the opinion that reduction in metabolism, irrespective of the factor or factors instrumental in its production, "is deleterious to the organism and tends to accelerate degeneration in the tissues." They have also observed that even though early degeneration is associated with low basal metabolic rates, more advanced degeneration tends to raise the rate. These investigators claim that there is an interference with utilization of foodstuffs by the tissues during the period of degeneration even though the individual is ingesting apparently adequate amounts of food.

ISLETS OF THE PANCREAS

That the Islets of Langerhans of the pancreas are not always the site of pathological changes in diabetes in man is apparent from post-mortem studies. Warren (60) found normal islet cells in 27% of cases. Wilder (61) claims that in 20 to 37 percent of cases of diabetes there is no anatomical explanation. Hartrift's (62) improved method—phase contrast microscopy—of studying the size of granules of beta cells, revealed in an equal number of diabetics and non-diabetic individuals with approximate averages of ages at death of 65 years, that 11% of the diabetic patients (46) in the series had normal islets. After microscopic examination according to Hartrift's method 6 of the 46 non-diabetic cases were classified as "diabetic." Five of the six were in the category diagnosed by re-

duplication of the basement membrane of and one was identified by advanced hydropic change of beta cells. In spite of the microscopic findings in the last case he was unable to find diabetic symptoms in the clinical record. Thus in his conclusion he states that he observed lesions of the islets in 41 of the 46 diabetic cases and in only 4 of the 46 non-diabetic patients.

According to Warren and LeCompte (53) hyalinizations of the islets of the pancreas is considered the most typical lesion in diabetes mellitus. They observed the occurrence of hyalinization to a greater or less degree in 41 percent of their cases of diabetes. They noted an increase in frequency of hyalinization as its severity becomes more marked. They concluded that the hyalinization of the islands is a cause and not a result of diabetes.

They have been able to demonstrate 33 percent normal pancreas as among 811 pancreases of diabetic persons as far as could be determined by ordinary histological methods in their series of studies. They admit that the existence of these normal islands in diabetes has been a puzzle to pathologists, especially when one observed diabetes with normal islets present in a disease that persists as long as life itself. Upon the basis of these observations they advance 4 hypotheses: "(1) the islands may be normal and insulin may be produced, but it is either defective in quality or neutralized by some substance in the body; (2) the islands may be normal but their secretory activity inhibited; (3) the diabetes may be of other than insular origin; (4) the insulin may be formed normally by normal islands but through failure in transport the insulin is not brought into the blood stream and so not disturbed to where its effects are needed." They apparently favor the third hypothesis. Substantiating this latter hypothesis they present cases of diabetes absolutely identical with one another clinically but with an absence of structural evidence of damage in the islands of Langerhans in one group, whereas, in the others, evidence of marked injury of various types exist.

They conclude from their studies that "suggestions regarding the etiological sigificance of such factors as other endocrine glands or the liver must remain partly speculative."

In their tabulated results of the lesions of the islands in 200 non-diabetic pancreases they observed practically all the lesions involving either the island tissue or the acinar tissue, or both, that are described in diabetic individuals, although with less frequency in non-diabetic individuals.

They conclude that "the occurrence of any of the generally accepted insular lesions may be considered as presumptive evidence of diabetes."

Since there are many different methods of affecting pancreatic islets and thus inducing diabetes it is believed that genetic, hormonal and dietetic factors may all directly or indirectly affect carbohydrate metabolism by influencing a single enzyme system or at least only a few such systems in islet cells.

Wrenshall and his associates (63) clarify the widely used expression; "insulin content of pancreas." They are of the opinion that there is proof that the insulin extracted from the pancreas by any method represents the total amount of insulin within the pancreas. They have advocated a more accurate expression, "insulin extractable from pancreas" to describe the active insulin obtained from pancreatic tissue. They also make the point that the extractable insulin, "can be represented as a metabolic pool in or near dynamic equilibrium between production of insulin on the one hand and its release into the blood stream or functional disappearance on the other." They noted the presence of diabetes to be associated with a lower average extractable insulin of pancreas than that in controls from the same assigned cause. They found the average extractable insulin of pancreas to "increase continuously with age at death from very low values, in relation to controls, in young diabetic patients, to a shallow maximum amounting to half of the control levels in diabetic patients dying in the fifth decade of life."

RETINOPATHY

Moreu's (64) studies of the pathogenesis and treatment of diabetic retinopathy revealed no relationship between retinal lesions and blood sugar level. He is of the opinion that diabetic retinopathy may continue to progress with a normal blood sugar level. He advised against the routine use of insulin for retinal complications because of the fact that in insulin induced hypoglycemic states in animals anatomico-pathologic changes of a circulatory type occur in the cornea, anterior chamber, uvea and retina. He has observed similar but less pronounced and less extensive changes with carbohydrate free diets, thus emphasizing the danger of insulin in producing circulatory changes which may lead to anatomic changes.

Dolger (65) concludes from his observation of 200 diabetics examined regularly for the past 25 years that the present day treatment of diabetes has failed to avert the accelerated vascular damage. Croon and Scott (66) claim from their observations that vascular or retinal changes could not be correlated with the severity or the control of the diabetes.

Guiliani (67) believes that retinal hemorrhage represents only the prelude to a whole picture of vascular degeneration which will slowly and progressively become generalized and which may have multiple repercussions at the expense of a variety of organs or systems. Mollerstrone (68) concludes from his observations that the cause of diabetic retinitis is unknown and that insulin therapy is no protection against it.

Day (69) is in agreement with other investigators that diabetic retinopathy is unrelated to the severity of the diabetes, age of the patient or degree of insulin regulation. He is of the opinion that the clinical aspects of the disease are puzzling and often appear contradictory. Goodby and Jacobs (70) conclude from their survey of 602 diabetics that the control of diabetes is without effect on the incidence of the long term complications of hypertension, retinal and lens changes and vascular disease. It is their opinion that "control" of diabetes is not synonymous with treatment of the underlying pathological condition which causes the metabolic defect and the vascular and eye changes which

may accompany it. Kennedy and Krechbaum (71) observed retinal hemorrhages in 62.4 percent of their 133 cases of both known and newly discovered diabetes. They observed that retinal hemorrhages increased in frequency with age, hypertension and the duration of the diabetes. Ashton (72) observed that micro-aneurysms are found in 33 percent of non-diabetic conditions and are not pathognomonic for diabetes. Saskin and his associates (73) conclude that at present there is no satisfactory treatment that will reverse or halt the trend of ocular conditions in diabetes. They believe that diabetic retinopathy is an integral part of the disease rather than a complication.

Hagedorn (74) admits the occurrence of retinitis or nephropathia in some well compensated cases of diabetes "after a far shorter time than some very badly compensated cases."

Wagner (75) admits that retinopathy continues to be a serious menace to the diabetic; he has observed an increasing frequency of its occurrence especially in the younger age group. He has noted no factor specific for its occurrence, nor any preventable or removable condition of its occurrence. He believes, however, that there may be some inherent factor in diabetes responsible for its development. He finally concludes from his studies that present day therapy of diabetes is unsatisfactory as far as the prevention of complications is concerned. He feels that there is a need for revision or amplification of therapy.

KIMMELSTIEL-WILSON SYNDROME

Kimmelstiel and Porter (76) claim that in most instances diabetes precedes intercapillary glomerulosclerosis. The treatment of diabetes according to them has no bearing on the development of intercapillary glomerulosclerosis. There exists no consistent relationship between intercapillary glomerulosclerosis and hyalinzation of the islands of Langerhans. They are of the opinion that arteriosclerosis roughly parallels the severity of intercapillary glomerulosclerosis but that the relationship may be coincidental.

Laipply and his associates (77) observed no demonstrable relationship between the degree of intercapillary glomerulosclerosis and the duration or degree of diabetes.

Rogers and Robbins' (78) comparison of 100 diabetics with proved intercapillary glomerulosclerosis and 176 diabetics not having this glomerular lesion revealed no significant difference in the severity of the diabetes. They claim that about one of every 4 diabetics will show intercapillary glomerulosclerosis at postmortem examination. They are of the opinion that the disease is correlated with the duration of diabetes but that the frequency of its occurrence does not appear to be correlated with the severity of the diabetes. They have observed that most of the patients with intercapillary glomerulosclerosis have mild diabetes, as judged by daily insulin requirement. In most instances it was observed that glycosuria was miniminal in spite of the marked hyperglycemia.

They conclude from their findings that many or most of the cases of intercapillary glomerulosclerosis do not have the classic clinical triad—edema, albuminuria (3-4 plus) and some degree of hypertension—since they found it in only 25 of 100 patients with intercapillary glomerulosclerosis. In addition, a few of their diabetics had the classic clinical pattern without intercapillary glomerulosclerosis. In subsequent studies Robbins and his associates (79), in identifying intercapillary glomerulosclerosis by histologic criteria, concluded "that the Kimmelstiel-Wilson lesion is a specific histologic lesion found only in diabetes."

Bell (39) interprets intercapillary glomerulosclerosis as a severe form of arteriosclerosis with extension into the glomeruli."

McManus' (80) interprets the absence of glycosuria and hyperglycemia in cases of intercapillary glomerulosclerosis as representing diabetes in remission or indicating another related but somehow different metabolic disorder supplanting the diabetes mellitus.

Upon the basis of renal lesions at autopsy and the metabolic records of 190 patients Zubrod and his associates (81) differentiate the diabetic with the Kimmelstiel-Wilson lesion from those with other types of renal lesions and those with no renal lesion. As a criterion for the diagnosis of the Kimmelstiel-Wilson lesion they used the "lumpy-loop" or hyaline mass in the glomerulus uniquely associated with diabetes. They observed diabetes to be less severe in patients with Kimmelstiel-Wilson disease as judged by the daily insulin dose than in other diabetic patients during the midphase and terminal of the diabetes even though the basal or the initial daily insulin dose was as much as that of the other two controlled groups.

In fact they noted that the diabetic requiring increasing amounts of insulin over a period of years did not develop the Kimmelstiel-Wilson syndrome. They noted that a severe diabetes became less severe, requiring decreasing doses of insulin and even then manifesting hypoglycemia, during the development of Kimmelstiel-Wilson syndrome. They also claimed that diabetic acidosis was so rare in this condition as to suggest a metabolic variation from ordinary diabetes.

These findings are in agreement with our own. We have seen some patients with Kimmelstiel-Wilson syndrome, formerly taking large daily doses of insulin (50-100 units) discontinue the insulin with the progression of the renal syndrome, even when glucose was given intravenously, become less severe with the progression of renal impairment or pathology. This has inspired one of us to study the relationship. It is interesting to observe, however, that one of the assistants, Neubauer, working with a new type of therapy—oral and intravenous administration of hypertonic sodium lactate along with marked dietary restriction of protein, supplemental administration of calcium and nonspecific symptomatic measures, observed a marked recession of the diabetes along with the improvement or partial restoration of renal function in a case subsequently proven to have the Kimmelstiel-Wilson syndrome. These latter findings in a group of cases will be published in complete detail in another paper.

INTERPRETATION OF DIABETES MELLITUS

Downe (82) believes from his observations that diabetes today should be thought of as a symptom com-

plex resulting from any of several causes rather than as a disease sui generis.

Cahn (83) is of the opinion that diabetes is to be considered as a syndrome of varied origin and symptomatology rather than as a definite clinical entity. Debenedetti and his associates (84) have observed that diabetics of mature age have spontaneous regression of hyperglycemia and glycosuria but with gradual increase of vascular disturbances. Bruch (85) believes there are various factors involved in the pathogenesis and clinical picture of diabetes mellitus. He is of the opinion that this will become more apparent when a more thorough investigation of one or several insulin destroying principles is made. Apparently the work of Burger and his associates (86), using crystalline insulin (0.14 mg. to 4 c.c. of blood) has shed much light on the multiple factors involved in the inactivation of insulin. In normal persons the inactivation of insulin through blood proceeds more rapidly with advancing age. Thus, in healthy persons under 20 years of age, the average inactivation time was 28 to 32 hours, in healthy persons 20 to 60 years of age, it was 23 to 26 hours, and in healthy persons over 60 years it was 20 to 22 hours. In patients with diabetes it was 9 hours; in patients with leukemia (with a white cell count of greater than 100,000) it was 2 to 3 hours. Bruch (85) claims that even though, "the insulin-destroying activity of the blood has been overshadowed by the newer knowledge of the role which is played by the tissues, especially the liver, the former must not be overlooked; as it was shown that this action of the blood increases considerably with age and specified pathologic conditions."

Barr (87) believes the clinical state of diabetes is a complicated situation in which a multitude of factors are in evidence at any particular time. He is of the opinion that the true nature of the disease is still in doubt.

Chisena (88) in his studies of renal disorders in diabetes sums up the subject by claiming that, "the anatomical aspect of diabetes has proved a perplexing problem, for diabetes does not appear to be associated with any consistent or distinctive lesion. Clinically, however, many different manifestations are produced, a great majority involving the kidney, and when these have been satisfactorily explained, we may be able to obtain a crystallization of the pathology in diabetes."

Volk and Lazarus (89) decline to believe that diabetes is based solely on primary insulin deficiency but provide a clinical means of distinguishing three pathogenetic factors of the diabetic syndrome, hepatic dysfunction, over-activity of insulin antagonists and, by exclusion, primary insulin deficiency.

Meyer (90) is of the opinion that diabetes in the aged is generally arteriosclerotic in origin and advises diet with sufficient carbohydrate and some glycosuria rather than a restricted carbohydrate diet.

Grorud (91) observed 50.17% of diabetics to have hypertension, and concludes that since diabetes and its associated essential hypertension have many endocrine implications and predisposing factors in common, abnormal endocrine interrelationship and functions should be considered in their etiology.

It is claimed that patients with hemochromatosis, a type of diabetes due to insulin deficiency, have never been observed to develop retinitis, and according to some investigators, rarely develop arteriosclerotic and renal changes or gangrene (92). Since the absence of insulin in hemochromatosis does not cause the above complications it is believed that some factor other than insulin lack is responsible for them in ordinary diabetes (92).

Since there are many different methods of inducing diabetes by affecting pancreatic islets it is believed that genetic, hormonal and dietetic factors may all directly or indirectly affect carbohydrate metabolism by influencing a single enzyme system or at least only a few such systems (93).

Some (94) describe two types of diabetes, one represented by the young, thin patient with marked insulin sensitivity and tendency toward ketosis. This group is usually free from vascular disorders—as represented by heart, eyes and kidney for some period of time after development of diabetes. The other group, which is represented by the middle aged, obese patient, usually with vascular, renal and ocular complications but has no tendency toward ketosis and relative insensitivity to insulin.

Somogyi (95) believes the ensuing changes in the blood sugar following the injection of insulin do not represent the action of the injected insulin. "The . . . course of the blood sugar curve reflects the quantitative relationship between insulin and its antagonists rather than the potential actions of the supply of active insulin." He believes that insulin action resulting from successive insulin doses exerts considerably less hypoglycemia effect than the first dose. The insulin action may be completely cancelled by the antagonistic factors which he claims accumulate when hypoglycemia is allowed to persist for some time.

Stainsby and Collins (96) are of the opinion, based upon an analysis of 250 consecutive cases of diabetes, that mild hyperglycemia without signs of ketosis or other unfavorable symptoms is harmless to patients. They warn against insulin reactions in elderly diabetics.

Thannhauser (97) is of the opinion that, "the primary disturbance in diabetes mellitus is to be found in a partial failure in the sugar molecule to be disintegrated in intermediary metabolism, and that gluconeogenesis is a result of and not a primary factor in the cause of diabetes." He concludes that insulin does not act directly on gluconeogenesis but affects the utilization of sugar in intermediary metabolism.

Houssay's (98) interpretation of diabetes is that it is a "disturbance in the endocrine equilibrium between the secretion of insulin on one hand and the secretions of the anterior hypophysis, adrenals and thyroid on the other." He claims the production of sugar by the liver and its utilization by the tissues, especially the muscles, is regulated by this equilibrium. In his description of the anterior hypophysis he mentions the physiological role of the hormonal substance or substances that regulate the carbohydrate metabolism as not being the cause of diabetes but necessary for the establishment of severe diabetes.

Goldberg and Lisser (99) gave the incidence of hyperglycemia with or without glycosuria in acromegaly as ranging from 11 to 40 percent. They are of the opinion that a different mechanism may be at work for the production of diabetes in acromegaly than in the primary pancreatic diabetic. Further elucidation of the problem according to them may change our present concepts of ordinary diabetes. For practical purposes acromegalic diabetes is treated in the same manner as diabetes in general.

Goldner (100) noted a marked, rapid and persistent post-operative improvement of the disturbed carbohydrate metabolism following the removal of an endocrine tumor of adrenal medullary tissue (pheochromocytoma) in a patient with diabetes. This latter finding he claims is an argument against the possibility that the diabetes was a purely coincidental and independent disease. He is of the opinion that the relatively high dose of insulin required in such a patient points toward extrapancreatic factors as contributory to the occurrence of hyperglycemia and glycosuria, considering "overactivity of epinephrine causing increased glycogenolysis in the liver" as the initial step in this mechanism. Thus he claims that as long as the hormone secreting tumor was present the hyperglycemia was aggravated.

Williams (101) is of the opinion that the diabetic metabolizes glucose efficiently when the blood sugar level is within the normal range or slightly above. An abnormally low blood sugar after food ingestion and insulin injection, according to Williams, is indicative of wasted insulin. His evaluation of blood sugar determinations emphasizes their usefulness during periods of active digestion whereas he considers the fasting blood sugar examination of only academic interest. It is in early stages of acute diabetes or acute hepatitis that fasting blood sugar determinations may be of value in measuring pancreatic or liver damage and recovery, but they are of no help as a therapeutic guide when injury becomes permanent.

He is of the belief that the metabolism of glucose cannot be determined or measured by blood sugar studies. "Every clinician of experience frequently sees patients who on carefully controlled diets carry persistently high blood sugar levels, yet remain essentially urine sugar free. It is fatuous to attempt the evaluation of therapeutic procedures in diabetes by blood sugar tests alone."

He considers that the use of Benedict's qualitative solution as a method of measuring glucosuria and plotting the result in plus signs is to be deprecated. "It is grossly inaccurate and misleading."

"Finally, the clinical well-being of the patient is an important therapeutic index. . . . Too much importance should not be attached to laboratory tests. Many patients may go for years with persistent glycosuria and high blood sugar and present no appreciable evidence of harm therefrom. Insulin confers a benefit on diabetic patients not measurable by laboratory tests. With it they live in fair comfort regardless of the varying prevailing theories and practices. Without insulin they invariably retrogress and die.

". . . Before new preparations of insulin are launched on the market, . . . clinicians and scientists . . . should set up a more definite and convincing set of standards of evaluation than now exists."

Best (102) defines diabetes, "as a disturbance of carbohydrate, fat and protein metabolism due to an imbalance of the glands of internal secretion." "Experimentally, all permanent diabetes is characterized by absence or deficiency of normal beta cells of the islands of Langerhans. . . ."

"A great deal of evidence indicating a deficit of insulin is available in many cases, but we want a satisfactory method of determining insulin in blood before we can seriously embark on the search for the diabetic who has his disease in spite of a normal endogenous supply of the hormone. . . . But we do hope, some day, to make the "ideal" insulin, which will be liberated only in response to need, so that the diabetic will never have hypoglycemia or hyperglycemia."

Conn (103) claims, . . . "By the time the patient shows the diagnostic criteria of the existence of the diabetic state he is presenting in most instances, an irreversible lesion characterized by inability of the pancreas to produce sufficient quantities of insulin for his needs. The damage has already been accomplished. The factors responsible during the preceding months or years for inciting the vicious cycle which led to pancreatic damage may no longer be present. . . . The etiology of diabetes must be studied before the existence of the disease." . . .

Krag (104) states, "It appears as if diabetes as it occurs in the juvenile, middle aged, and aged varies in some respects and that several etiologic factors may be of importance. In the juvenile individual the disease is usually abrupt in onset, severe, more difficult to control, more frequently complicated by coma, acidosis and hepatomegaly, rarely preceded by obesity and degenerative changes and the relationship of heredity is more clear cut." He is of the opinion that experimental results in animals, and in some instances in man, have revealed a multiplicity of factors that may produce diabetes.

Recht's survey of 31 patients with juvenile diabetes of 10 years duration revealed no demonstrable relation between the incidence of complications and control of the diabetes or type of diet. John (106) claims that if a diabetic is hyperglycemic only 25 to 30% of each day one should consider him as satisfactorily controlled.

That diabetes does not play any role in the occurrence of hyperglycemia in acute coronary thrombosis was shown by the observations of Ellenberg and his associates (107). They believe it is a manifestation of shock and have shown that the hyperglycemia is accompanied by central liver cell necrosis.

According to Tolstoi's (31) observations of the past 4-5 years hyperglycemia has failed to cause decompensation of insular tissue as commonly believed, nor has it favored or accelerated the development of degenerative vascular disease.

Mirsky (108) admits that the etiology of diabetes in man is apparently unknown. He claims, however, that pancreatic abnormalities observed in some patients with diabetes may be attributed to insulin insufficiency, whereas in others they must be attributed to unknown factors which may also be causative factors for the extremely common associated renal and vascular damage.

Bell (109) believes that diabetes is a functional

disturbance of the islet cells and not a destructive lesion. The minor changes indicative of decreased activity noted in the beta cells according to Bell are not due to a primary degeneration but point to some injurious substance in the circulating blood.

Collens and his associates (110) conclude from their studies of peripheral neuritis that there is no apparent relationship between the degree of neuritic involvement and the duration, intensity, or degree of control of diabetes.

A more recent study tends to support the view that diabetes is not a causative factor in vascular or retinal disorder is apparent from the worker of Shropshire and his co-workers (111) in the non-surgical treatment of cataract—the administration of fish lens protein extract. They observed subjective improvement in a group of 14 patients between 60 and 70 years old suffering from typical senile opacities. Several of the patients' eye conditions were associated with diabetic hypertension or arteriosclerosis or had combinations of these conditions. They noted a clearing of lens opacities, and retinal detail.

That there is an unconscious trend toward maintaining compatible hyperglycemia in diabetic control is evident from an answer to an inquiry which appeared in the Journal of the American Medical Association on June 23, 1951 (112) concerning control of diabetes in employees, which states: "A reasonable and safe range without specifying exact figures for blood sugar values would be 130 to 200 mg. per 100 c. c. venous blood, Folin-Wu, before meals. Standards would be before meals. Standards would be stricter if the patients worked with machinery. Permission would be refused to engage in hazardous work involving safety of others. These standards are stated somewhat liberally but they provide a margin of safety, and yet reflect fairly good control of diabetes."

CONCLUSIONS

I. The true etiology of premature arteriosclerosis in diabetes is unknown.

II. The results of our statistical and clinical survey revealed the following:

(1) the apparent known duration of diabetes plays no role in the incidence of vascular complications, (2) that there is no relationship between blood sugar levels and complications (3), and that there is no relationship between the average insulin dose and "vascular complications."

III. That the two existing schools of therapy for diabetes, namely, the laboratory and the clinical schools, should be supplanted by the compatible school, which permits the physicians to use both the clinical and the laboratory findings in guiding his patient's therapy, without placing undue emphasis on either one for the following reasons:

1. A normal post prandial blood sugar level for the diabetic according to the compatible method is the level most compatible to his well being depending upon (1) age, (2) condition of the cardiovascular system, (3) occupation, (4) existing complications, (5) insulin and (6) activities. This compatible post prandial level in patients taking insulin is generally considered to be 170-220 mg. per 100 c.c. of whole blood. If the patient is not upon insulin, the compatible blood sugar level may be lower.

2. Contrary to the general belief that hyperglycemia is harmful, compatible post-prandial hyperglycemia was observed to be protective. This was noted in the studies of 100 patients under our personal supervision which revealed that

(a) 53 or 53% were able to discontinue insulin for the past average period of 2 years and 8 months, varying from 2 months to 9 years and 6 months for the individual patient. This group had been on insulin therapy for a variable period of 2 days to 3 years and 5 months for the individual patient, with an average duration of 4 months and 20 days.

(b) Of the remaining 47 patients, 24 after having been upon insulin therapy for an average period of 5 months, varying from 3 weeks to 2 years for the individual patient, discontinued it for an average period of 9 months, varying from 8 days to 3 years for the individual patient. Insulin therapy was resumed and has been continued for the past average period of 13 months, varying from 2 months to 3 years for individual patients. Apparently the insulin mechanism was little affected by the non-insulin interval as evidenced by the average insulin dose of 18 units for the second insulin period, an increase of only 4 units as compared with the initial insulin therapy dose of 14 units.

(c) In 23 patients of the group, diet therapy was first prescribed for an average period of 2 years ranging from 4 weeks to 7 years and 9 months for the individual patient after which insulin therapy was instituted for an average period of 1 year and 5 months, varying from 4 months to 3 years for the individual patient. The average daily insulin dose was 19 units, ranging from 12 to 32 units for the individual patient.

3. There was a decreased incidence of hypoglycemia reactions in insulin-treated patients.

4. Normoglycemic fasting blood sugar levels are inadequate evidence of diabetic control. It should be combined with post prandial blood sugar estimations as described in the compatible method.

5. Irrespective of the type of therapy in the above group of 100 as well as in another group of 100 patients who were treated by diet alone, associated vascular disorders were prevalent not only upon their initial visit but also during our therapy.

IV. There exists no statistically significant necessary relationship between the control of diabetes and vascular degeneration. This opinion appears to be shared by an increasing number of clinical investigators and laboratory workers, as revealed by the review of the literature.

From their observations they believe that:

1. The control of glycemia does not check the progress of vascular degeneration (39, 41, 45).

2. No physician can promise a patient that control of glycemia can forestall the progression of degeneration (43, 44).

3. Diabetes of long standing does not necessarily result in severe atherosclerosis (52).

(a) No explanation can be given for the absence of extensive premature vascular disease in poorly controlled diabetes of long duration and its presence in well controlled cases of diabetes of shorter duration (55).

4. The islets of Langerhans are not always the site of pathological changes (60, 61).

5. There exists no relationship between retinal lesions and blood sugar level (64, 66). Progression of retinopathy has been observed in the presence of normal blood sugar.

6. Treatment of diabetes mellitus has no bearing upon the development of intercapillary glomerulosclerosis (76). Observations have revealed no demonstrable relationship between the degree of intercapillary glomerulosclerosis and duration and severity of diabetes (77). We observed a decreased severity of diabetes with the progression of renal pathology as well as improvement or restoration of renal function on newer methods of therapy.

7. Present day diabetic therapy is unsatisfactory in relation to the prevention or deceleration of premature arteriosclerosis.

V. We believe that diabetes is a syndrome or a symptom complex with a varied etiological background.

VI. Physicians should cease frightening their patients with compatible post-prandial hyperglycemia. This may exist with or without glycosuria. They should enlighten the patient concerning the facts or theories of vascular disease (113). They should emphasize the importance of laboratory results only in conjunction with the patient's physical condition as advocated by the compatible school.

VII. Physicians should subject their patients with diabetes to a thorough laboratory and physical examination for associated vascular or organic disorders.

VIII. We conclude, therefore, that a postprandial blood sugar of 240 mg. (2 hours after breakfast and insulin) as discussed in our initial survey is innocuous and should cause no alarm.

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REFERENCES

1. Sindoni, A. Jr.: Protamine Insulin vs. Ordinary Insulin, J. A. M. A., Vol. 108 April 17, 1937, 1320-27.

2. Sindoni, A. Jr.: Blood Sugar vs. Urine Sugar, J. A. M. A. Vol. 112, 2503-8, June 17, 1939, June 24, 1939, Vol. 112, 2595-2600.

3. Sindoni, A. Jr.: Pregnancy and Diabetes Mellitus, Health Bulletin, Dept. Public Health, Phila., Pa., March, 1941.

4. Sindoni, A. Jr.: Present Day Conception of Protamine Zinc Insulin and Globin Insulin with Zinc. Delaware State Med. Jour., Feb. 1946 (1-12).

5. Sindoni, A. Jr.: Fasting vs. Post-prandial Blood Sugar as Observed in Normal Individuals, Medical (non-diabetic) Patients and Patients with Diabetes. Amer. Jour. Digest. Diseases, Vol. 13, 178-192, June 1946.

6. Sindoni, A. Jr.: An Unusual Diabetic Coma in a Child with Recovery with special reference to Insulin Resistance and Hypopotassemia. Amer. J. Digest. Diseases, Vol 17, 1950. 406-8.

7. Anderson, G. E.: A Creed for the Treatment of Diabetes. Amer. Jour. Digest. Diseases, Vol. 14, May 1947, 170-176.

8. Handelsman, M. B.: Discussion of Anderson's paper, 177-178—A Creed for the Treatment of Diabetes. Amer. Jour. Digest. Diseases, Vol. 14, May 1947, 177-178.

9. Paullin, J. E.: Treatment of Diabetes Mellitus—Special Article—Modern Medicine—Jour. of Diagnosis and Treatment. May 1, 1947, Vol. XV p. 35-38. Paper given before Interstate Post-Graduate Med. Assoc. of North America, Cleveland, Oct. 15-18, 1946.

10. Richetts, H. T.: Does Hyperglycemia Harm the Diabetic Patient? The Medical Clinics of North America. 267-277. W. B. Saunders Co., Phila. & London, 1947.

11. Boyd, J. D., Jackson, R. L. and Allen, J. H.: Avoidance of Degenerative Lesions in Diabetes Mellitus. J. A. M. A., Vol. 118, Feb. 28, 1942, 694-696.

12. Beaser, S. B.: Clinical Characteristics of Early Diabetes Mellitus. New England Jour. Med., 239:765 (Nov. 18) 1948.

13. John, H. J.: Treatment of Diabetes Mellitus without Regard to Hyperglycemia and Glycosuria. Amer. Jour. Dig. Diseases, Vol. 10, 129-131, April 1943.

14. Anderson, G. E.: Diabetes Mellitus, Its Modern Interpretation and Treatment. Bull. M. Soc. Co. Monroe, 5:327-29 (Jan. 1948).

15. Editorial: Management of the Diabetic patient. South Med. & Surg. 110:79-90, March 1948.

16. Mann, G. V., Gardner, C., Root, H. F.: Clinical Manifestations of Intercapillary Glomerulosclerosis in Diabetes Mellitus. The American Journal Med., July 1949, Vol. VII, 3-4.

17. Marble, A.: Present Day Treatment of Diabetes in the Prevention of Degenerative Complication. Jour. Arkansas Med. Soc., 44:69-73, Aug. 1947.

18. Weinstein, A.: Diabetes Mellitus. A Review of Progress. Jour. Texas Med. A., 40:220-225, July 1947.

19. Root, H. F.: Diabetes and Vascular Disease in Youth. Amer. Jour. Med. Sc., 217:545, May 1949.

20. Wilson, J. L., Root, H. F. and Marble, A.: Controlled versus Free Diet Management of Diabetes. J. A. M. A., Vol. 147, Dec. 15, 1951; 1526-1529.

21. Sherrill, J. W.: Diabetic Retinitis. The Relationship between retinal degenerative changes and the degree of diabetic control. Bull. of the Scripps Metabolic Clinic, Vol. 2, No. 6, Oct. 1951, La Jolla, San Diego, Calif.

22. Peck, F. B.: The Insulin in Diabetes. Modern Medicine 64, 1949.

23. Millard, E. B. and Root, F. H.: Degenerative Vascular Lesions and Diabetes Mellitus. Am. Jour. Dig. Diseases. Vol. 15, 1948, Feb., 41-51.

24. Woerner, C. A.: Studies of the Islands of Langerhans after continuous intravenous injections of Dextrose. (Anat. Rec. 71:33, 1938).

25. Best, C. H., Haist, R. E. and Ridout, J. H.: Diet and the Insulin content of Pancreas. Jour. Phys. 97:107, 1939.

26. Haist, R. E. and Best, C. H.: Factors affecting the insulin content of Pancreas. Science, Vol. 91, April 26, 410, 1940.

27. Lukens, F. D. W. and Dohan, F. C.: Pituitary Diabetes in the Cat; Recovery following Insulin or Dietary Treatment. Endoc., Feb. 1942, Vol. 30, 175-202.

28. Dohan, F. C. and Lukens, F. D. W.: Experimental Diabetes Produced by the Administration of Glucose. Endoc. April 1948, Vol. 42, 244-262.

29. Harron, S. Steven and State, David: Effect of prolonged intravenous administration of dextrose on beta cells of islets of Langerhans. Arch. Path. 48:297-304, Oct. 1949.

30. Tolstoi, E.: Treatment of Diabetes Mellitus by the Clinical Approach. Medical Clinics of North America. Nation Wide Number (485-494), W. B. Saunders Co., 1950.

31. Tolstoi, E.: Newer Concepts in the Treatment of Diabetes Mellitus with Protamine Insulin. Amer. Jour. Digest. Dis., 10:247-255, July 1943.

32. Sindoni, A., Jr.: Vitamin Deficiency in Prescription Diets of Diabetics. American Journal of Digestive Disease and Nutrition, Vol. III, No. 10, Dec., Pages 759 to 765, 1936.

33. Burchell, H. F.: Clinical Manifestations of Arteriosclerosis. J. A. M. A., Vol. 147, Dec. 15, 1951, 1511-1514.

34. Dunn, S. J., Sheehan, H. L. and McLetchie, N. G. P.: Necrosis of the Islets of Langerhans Produced Experimentally. Lancet, 1:484, 1943.

35. Goldner, M. G.: Alloxan Diabetes. Its Production and Mechanism. Bull. New York Acad. Med. 21:44, 1945.

36. Griffiths, M.: Uric Acid Diabetes. J. Biol. Chem. 172, 853, 1948. The Mechanism of the Diabetogenic Action of Uric Acid. J. Biol. Chem. 184, 289, 1950.

37. Lukens, F. D. W.: Pituitary Diabetes. Am. J. Med. Sc. 212:229-240, Aug. 1946.

38. Lukens, F. D. W. and Dohan, F. C.: Morphological and Functional Recovery of the Pancreatic Islands in Diabetic Cats treated with Insulin. Science, Vol. 92, Sept. 6, 1940, 222-23.

39. Bell, E. T.: The Pathological Anatomy of Diabetes Mellitus. Illinois M. J. 92:215-18, Oct. 1947.

40. Ducas P.: Late degenerative lesions of Juvenile Diabetes. Medicine 29:12-16, March 1948.

41. Hedges, R. N.: The Influence of Insulin on Degenerative Changes in Diabetes Mellitus. Illinois, M. J., 93:206-10, April 1948.

42. Moschovitz, E.: The Relation of Hyperplastic Arteriosclerosis in Diabetes Mellitus. Ann. Int. Med., 34:1137, May 1951.

43. Barr, D. P.: Russ, E. N. and Eder, N. A.: Protein-Lipid Relationships in Human Plasma. II. In Atherosclerosis and Related Conditions. Am. Jour. of Med., Vol. XI, July-Dec. 1951, 72-85.

44. Lukens, F. D. W.: Incentives to the Treatment of Diabetes Mellitus. Med. Clinic of North America, March 1947, Nation-Wide No.

45. Davidson, C. S.: Lewis, J. R., Tagnon, H. J., Adams, M. A. and Taylor, F. N. L.: Abnormal biochemical changes in patients with severe, acute medical illness with or without peripheral vascular failure. New Engl. Med. 234, 279, 9, 1946.

46. Dry, T. J. and Hines, E. A. J.: Role of Diabetes in the Development of Degenerative Vascular Disease. Ann. Int. Med. 14:1893, April 1941.

47. Ivy, A. C.: Drug Therapy in Degenerative Disease. J. A. M. A., Vol. 136, April 3, 1948, 909-911.

48. Stearns, S., Schlesinger, M. J. and Rudy, A.: Incidence and Clinical Significance of Coronary Artery Disease in Diabetes Mellitus. Arch. Int. Med., Vol. 80, 463-474, Oct. 1947.

49. Adlersberg, D., Parets, A. D. and Boas, E. P.: Genetics of Atherosclerosis. Studies of Families with Xanthoma and Unselected Patients with Coronary Artery Disease Under the Age of Fifty Years. J. A. M. A., Sept. 24, 1949, Vol. 141, 246-254.

50. Kirk, E., Chieffi, Margaret and Kountz, W. B.: The correlation between Thyroid Function and the Incidence of Arteriosclerosis. Jour. Gerontology, July 1949, Vol. 4, 212-217.

51. Katz, L. N., Mills, G. Y. and Cisneros, F.: Survival after Recent Myocardial Infarction. Arch. Int. Med., Vol. 84, Aug. 1949, 305-320.

52. Bell, E. T.: A Post Mortem Study of 1,214 Diabetic Subjects with Special Reference to the Vascular Lesions. Proc. of the Amer. Diabetes Association. Vol. 1-10, Annual Meeting 1950, 62-82.

53. Warren, S. and LeCompte, P. M.: The Pathology of Diabetes. Lea & Febiger, 3rd Ed., 1952.

54. Lukens, F. D. W.: The Possible Dangers of Hyperglycemia. Proc. of the Amer. Diabetes Assoc. Annal Meet., 1950. Index Vol. 1-10, 103-115.

55. Pillow, R. F. and Palmer, L. J.: Juvenile Diabetics. Northwest Med. Feb. 1949, Vol. 48, No. 2, 101-114.

56. Zisserman, L.: Diabetes Mellitus. A Survey of 155 Deaths in Diabetic Patients. Jour. Clinic. Endoc., April 1941, Vol. 1, No. 4, 314-315.

57. DeZoysa, V. P.: Clinical Variations of the Diabetic Syndrome in a Tropical Country. (Ceylon) Arch. Int. Med., Dec. 1951, Vol. 88, No. 6 (812-818).

58. King, W. E.: Pathological Aspects of Diabetes. Med. J. Australia. Jan. 20, 1951 (113-114).

59. Kountz, W. B. and Chieffi, Margaret: General Oxidative Processes with Relation to Degenerative Changes in the Body. Geriatrics, Nov.-Dec. 1947. Vol. 2, 344-357.

60. Warren, S.: Pathology of Diabetes Mellitus. Phila. Lea-Febiger, 1930.

61. Wilder, R. M.: Reflections on the Causation of Diabetes Mellitus. J. A. M. A. Dec. 9, 1950, 144:1234-39:

62. Hartroft, W. S.: The Islets of Langerhans in Man Visualized by Phase Contrast Microscopy. Proc. Am. Diabetes. 10:46, 1950.

63. Wrenshall, G. A.:—Bogoch, A. and Ritchie, R. C.: Extractable Insulin of Pancreas. Correlation with Pathological and Clinical findings in Diabetic and Non-Diabetic Cases. Diabetes—Jour. Amer. Diabetes Association. Vol. 1, No. 2, March-April 1952, 87-105.

64. Moreu, A.: Pathogenesis and Treatment of Diabetic Retinopathy. Arch. Soc. Ophth, Hispanean 9:139, Feb. 1949. (Abstr. from Arch. Ophth, 43:1108-9, June 1950).

65. Dolger, H.: Clinical Evaluation of Vascular Damage in Diabetes Mellitus. J. A. M. A. Vol. 134, Aug. 16, 1947 1289-91.

66. Croon, J. H. and Scott, G. I.: Retinal and Vascular damage in long standing diabetes. Lancet 256:555-558, 1949, April 2.

67. Guiliani, V.: Vascular Damage in Diabetes Mellitus. Diagnosi 4:200, March 1948.

68. Mollerstrom, J.: Occurrence of retinal eye complications in diabetes. Nord. Med. 36:2571, Dec. 19, 1947. Abst. from J. A. M. A., 137:1091, July 17, 1948).

69. Day, R.: The Problem of Diabetic Retinopathy. Sout. M. J. 44:549-51, June 1951.

70. Goodby, H. K. and Jacobs, J. H.: The Influence of the Control of Diabetes Mellitus on the Incidence of Long Term Complications. St. Thomas Hosp., Rep. 6:244-54, 1950.

71. Kennedy, R. J. and Krechbaum, F. M.: Ocular Fundus Findings in 133 Cases of Diabetes Mellitus. Cleveland, Clin. Quart 18:134-40, April 1951.

72. Ashton, N.: Normal Retinal Micro-aneurysms in the non-diabetic subject. Brit. Jour. Ophth. 35, 189, 1951.

73. Saskin, E., Waldman, S. and Pelner, L.: Diabetic Retinopathy. Am. J. Opth. 34:613-17, April 1951. Quoted by Diabetes Abs. 3rd Quarter Vol. 10, No. 3, July 1951, p. 145.

74. Hagedorn, H. C.: Post-War Problems in Diabetes. Proc. Amer. Diabetes. Assoc., 6:145, 1946.

75. Wagener, H. P.: Retinopathy in Diabetes Mellitus. Proceed Amer. Diabetes Association. Vol. 5, 1945, 203-216.

76. Kimmelstiel, P., Porter, W. B.: Intercapillary Glomerulosclerosis. New England J. Med. 238:908-12, June 24, 1948.

77. Laipply, T. C., Eitzen, O. and Dutra, R. F.: Intercapillary Glomerulosclerosis. Arch. Int. Med. 354-364, Vol. 74, Nov. 1944.

78. Rogers, J., Robbins, S. L. and Jeghers, H.: Intercapillary Glomerulosclerosis. A Clinical and Pathologic Study. II. A Clinical Study of 100 Anatomically Proven Cases. Amer. Jour. Med. (Index No.), June 1952, Vol. XII, 692-699.

79. Robbins, S. L., Rogers, J. and Woolenman, O. J.: Intercapillary glomerulosclerosis: A Clinical and Pathologic Study. III. A Pathologic Study of 100 Cases. Amer. Jour. Med., June 1952, Vol. XII, 700-705.

80. McMamus, J. F. A.: The Development of Intercapillary Glomerulosclerosis. Proc. Amer. Diabetes Assoc., 1949, Vol. 9, 303-306.

81. Zubrod, C. G., Eversole, S. L. and Danna, G. W.: Amelioration of Diabetes and Striking Rarity of Acidosis and Patients with Kimmelstiel-Wilson Lesions. New England J. Med., 245, 518-525, Oct. 4, 1951.

82. Downe, E.: Etiology of Diabetes Mellitus. Med. Jour. of Australia 1:110, Jan. 20, 1951.

83. Cahn, T.: Evolution of Our Conceptions on the Pathogenesis of Diabetes. Press Med. 58:1024-26, Sept. 27, 1950.

84. Debenedetti, E., Aheri, V. and Viarengo, G.: Spontaneous Regression of Diabetes in Subjects of Mature Age. Minerva Med. 2:64-9, 1949. Abstr. from Excerpta Med. (Endoc.) 4:136, April 1950. Fr. Diabetic Abstr. second quarter, Vol. 10, No. 2, April 1951, p. 66.

85. Bruch, E.: Recent Progress in Insulin Physiology. Arch. Int. Med. Vol. 86, Sept. 1950, 427-443.

86. Burger, M.: Footnotes 26, 28 and 37 Burger M. and Kohl.: Arch f exper. Path. V. Pharmakol 174: 130, 1934 178:269, 1935. Cited by Bruch E.: Arch. Int. Med. Vol. 86, Sept. 1950, P. 440. Ref. No. 62.

87. Barr, D. P.: The Relationship of Endocrine Factors to the Development of Diabetes Mellitus. Smith, Kline & French Laboratories. The Clinical Problems of Advancing Years. Second Symposium pp. 26-27, 1951. Diabetes (Abst.) March-April, 1952. Jour. Amer. Diabetes Asso.

88. Chisena, F.: Diabetes and the Kidney. Med. Times. Vol. 76, June 1948. 250-252.

89. Volk, B. W., Lazarus, S. S.: A Clinical Study of the Pathogenesis of the Diabetic Syndrome. Amer. Jour. Digest Disease, Vol. 18, Sept 1951, 269-274.

90. Meyer, J.: Diet for the Aged. Geriatrics Vol. 2, May-June 1947, 149-154.

91. Grorud, A. C.: Hypertension and Diabetes. South Dakota J. Med. & Phara. 1:48-51, Feb. 1948.

92. Editorial: Newer Aspects of Insulin Action. Brit. M. Jour. 1:826, June 7, 1947.

93. Editorial: The Cause of Diabetes. Lancet 2:1016-17, Dec. 25, 1948.

94. Editorial: Two types of diabetes. Lancet, 2:722-23, Oct. 20, 1951. Diabetes Abst. 1952, March-April.

95. Somogyi, M.: Effect of Insulin Injections Repeated at Brief Intervals. End. Vol. 47, Dec. 1950, 436-442.

96. Stainsby, W. J. and Collins, A. P.: Diabetes Mellitus. An Analysis of 250 Cases and a Discussion of Simplified Procedures for Regulation. Penna. M. J. 50 (8) 808-811, 1947.

97. Thannhauser, S. J.: Studies on the Mechanism of Diabetic Disturbance Using the "Nitrogen Minimum excretion" as a Measure of Glyconeogenesis. Endoc. Feb. 1940, Vol. 26, 189-200.

98. Houssay, B. A.: Advancement of Knowledge of the Role of the Hypophysis in Carbohydrate Metabolism During the last twenty-five years. Endoc. Vol. 30, June 1942, 884-897.

99. Goldberg, Minnie B. and Lisser, H.: Acromegaly: A Consideration of Its Course and Treatment. Jour. Clin. Endoc. Aug. 1942, Vol. 2, 477-501.

100. Goldner, M. G.: Pheochromocystoma with Disease. A Case Report and Discussion. Jour. Clin. Endoc., Oct. 1947, Vol. 7, 716-723.

101. Williams, J. R.: The Clinical Evaluation of Insulin. Jour. Clin. Endoc., March 1945, Vol. 5, 151-154.

102. Best, C. H.: Symposium on Diabetes. Modern Medicine, June 1, 1949, 43-44.

103. Conn, J. W.: Current Research Problems in Diabetes. Modern Medicine, June 1, 1949, 49-52.

104. Krag, C. L.: Diabetes Mellitus in the Aged. Jour. Gerontology. Vol. 4, July 1949, 253-255.

105. Recht, L.: Late Juvenile Diabetes. Nordisk Medicine Stockholm. 46:1855, Dec. 12, 1951.

106. John, H. J.: Liberal Diets for Diabetic Patients. Modern Medicine, April 1, 1952, p. 71. Ann. Int. Med. 35: 1318-1328, 1951.

107. Ellenberg, M., Osserman, K. E. and Pollack, H.: Hyperglycemia in Coronary Thrombosis. Diabetes—Jour. Am. Diabetes Association. Vol. 1, No. 1, Jan.-Feb. 1952, 16-20.

108. Mirsky, I. A.: Some considerations of the etiology of Diabetes Mellitus in Man. Proceed. Amer. Diabetes Association (Fifth Annual Meet.) Vol. 5, 1945, 119-138.

109. Bell, E. T.: Text of Pathology 566; 1947 (Lea-Febiger) Phila.

110. Collens, W. S., Zilensky, J. D. and Boas, L. C.: Lack of Correlation Between Hyperglycemia and Diabetic Neuritis. Amer. J. Med., 1:638, Dec. 1946.

111. Shropshire, R. F., Ginsburg, J. R. and Mendel, Jacob: The Nonsurgical Treatment of Cataract. Science Vol. 116, 276-278, Sept. 12, 1952.

112. Answer to: Control of Diabetes in Employees. Queries and Minor Notes: J. A. M. A., June 23, 1951, Vol. 146, 767.

113 Sindoni, A., Jr.: The Diabetic's Handbook. The Ronald Press Company, New York, 1948.

IRON EQUILIBRIUM

CLINICAL OBSERVATIONS ON NUTRITIONAL ANEMIA

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SUITABLE foods and iron preparations used in nutritional anemia have their merit, but a review of the entire structure of the medical and dietary management of nutritional anemia demonstrates the value of incorporation of some of the newer findings in iron-deficiency human anemias. This paper will deal with the dietary implications that form a major sector of the medical management of nutritional anemia.

More than one etiological factor is involved in the production of an iron deficiency anemia, but some of the obvious ones are insufficient intake of protein, inadequate intake of minerals, particularly iron and the trace elements, infections and toxins, bleeding and inadequate dietary regimes due to certain therapeutic programs. The object of dietary management is to supply simultaneously all the members of the nutrient team in kind and amount necessary for the individual. Rapid growth with an increased blood volume is one reason for anemia of childhood.

In childhood the three main considerations are (1) protein (2) calories and (3) calcium. When anemia is present of the nutritional type then interrelated factors necessary to hemoglobin production are important: iron, trace elements, tyrosine, histidine, tryptophane, lysine and arginine. It is felt that the amino acids mentioned are diverted to blood building as well as other functions. The tryptophane requirement of infants is felt to be about five times more than that of an adult man. Lysine plays an important role in protein nutrition. A knowledge of the biological value of protein demonstrates the variation in composition of the internal composition of amino acids, and the need for a mixed and varied diet (1).*

Foodstuffs contain ferric hydroxide. It is the function of the secretions of the digestive tract to convert the colloidal materials into dispersed, utilizable ions. The ferric form is reduced to the ferrous form before absorption in the upper part of the duodenum. Vitamin C, and certain protein groups (sulfhydryl) assist in reducing ferric salts to the ferrous form. Microcytic hypochromic anemia develops when an adequate quantity of available ferrous iron is not available for hemoglobin production. Iron is needed for blood hemoglobin, the reticulo-endothelial system, and in the nuclei and cytoplasm of the stroma of cells (2, 3, 4, 5).

Milk diets have been implicated in iron-deficiency anemias in milk-fed infants. "An ascorbic acid deficiency favors a tendency toward pteroylglutamic acid deficiency in monkeys fed on these milk diets" (6). Milk is recognized to be a food which occupies the chief number of calories in most diets up to one year. The supply of iron in the infant may hold him until he can digest and absorb iron carrying foods but if these are not forthcoming then the hemoglobin level is affected. The B vitamins are interrelated with many other nutrients, for they are implicated in nutritional anemia when the protein supply is limited. Chief among the recently investigated B vitamins is Vitamin B_{12}* and the animal protein factor. The intrinsic factor of Castle is enzymatic in nature and combines with or alters vitamin B_{12} in such a way that it is not available for growth in the absence of the enzymatic factor. Enzymes undergo irreversible denaturation in very acid and very alkaline solutions. Sometimes individuals have been fed diets, foods and medications for long and extended periods that nullify the normal secretions and over-emphasize the alkaline materials, thereby lessening the valuable secretions in the gastrointestinal tract. Strong alkaline compounds frequently administered are contraindicated when iron therapy is being forced.

The catalyst of respiration is iron. The "unique protein ferritin is involved in a surprising number and variety of physiological phenomena, among which is that of maintaining homeostasis" (7). Narcotics inhibit the reducing systems. Dehydrogenase activity is a vital consideration in respiration. "A dehydrogenase (8) may be defined as an enzyme which activates certain hydrogen atoms of a metabolite so that they are capable of being transferred from the metabolite to a suitable acceptor."

The liver is the cite of some of the iron storage. Iron from liver ferritin can be mobilized for hemoglobin synthesis, but it is the duty of the diet to protect the liver cells so they can have their many functions at the highest level. Diets with liver protection as the cardinal principle contain (1) liberal amounts of the right kind of protein, amino acids and total nitrogen. Methionine and sulfhydryl groups are important in amino acid considerations. The methionine to cystine ratio is important also. Tyrosine must be supplied. Because of the interrelationship with phenylalanine and tyrosine, vitamin C must be present. Ascorbic acid is a hydrogen carrier. Ascorbic acid is interrelated to glutathione. Glutathione is known to prevent inactivation of the sulfhydryl groups of enzymes. Then (2) other factors. Anemia developing from feeding abnormally low amounts of protein: Total grams of pro-

*The U. S. Dept. of Agri. list some of the following foods as capable of carrying into the diet some of the necessary items: dried apricots, common or kidney beans, lima beans, mustard greens, New Zealand spinach, dried peaches, sorgo sirup, soybeans, spinach, beet greens, broccoli leaves, chard, cowpeas, dandelion, eggs, kale, dry lentils, molasses, turnip greens, watercress, wheat bran, whole barley, snap or string beans, brussels sprouts, cabbage, collards, whole-ground cornmeal, dates, dock or sorrel, endive or escarole, dried figs, leaf lettuce, oatmeal or rolled oats, green or dried peas, dried prunes, whole rye flour, seedless raisins or currants, sugar cane sirup, vegetable oyster or salsify, whole wheat cereals, whole wheat flour.

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*Vitamin B_{12} has many interrelationships with the level of protein in the diet, methionine, glycine, choline, betaine, folic acid, ascorbic acid, pantothenic acid. J. Biological Chemistry p. 141 (Sept.) 1951.

tein, total grams of amino nitrogen, total grams of amino acids must be distributed throughout a variety of food groups because of the more than four dozen important nutrients that must be supplied in the balanced ration when all metabolic requirements are met simultaneously. In evaluating the protein the reviewer must recognize (1) the net protein, (2) egg replacement value and the so-called chemical score, (3) chemical composition and concentration of protein in a given portion of food, (4) biological value for a given species, (5) utilization and fabrication value in the metabolic pool, (5) limitations and delimiting factors.

The liver is protected by protein and carbohydrate calories. Carbon sources of a suitable nature undergo phosphorylation. Glucose-L-phosphate is an intermediate in the synthesis and breakdown of glycogen in the liver cells. It has been demonstrated that pyridoxal phosphate is the coenzyme for transaminases, and a variety of amino acid decarboxylases and for tryptophanase. Biotin is a component of a coenzyme or coenzymes with many functions. Protein calories should not be the direct and chief source of calories or protein will be directed to functions of lesser importance than that of carrying nitrogen. Convalescence may be slow due to insufficient caloric intake, nitrogen rejection and insufficient protein intake or lack of key amino acids like methionine. Three parts of methionine equals one part of choline in lipotropic activity. Cystine plus choline can only replace one-fifth of the methionine. Coenzyme A is an acetylation cofactor; coenzyme A is the coenzyme for the enzyme in nervous tissue which is involved in the synthesis of acetyl choline. Coenzyme A is then a part of this picture and ten percent of coenzyme A is pantothenic Acid, William's discovery. Vitamins associated with the anemia of vitamin deficiency diseases are Pyridoxine, Niacin, Folinic acid, Vitamin B_{12}, Riboflavin, Pantothenic Acid, Animal protein factor, Thiamine.

Lipotropic agents of note are inositol, betaine, choline, B_6, B_{12} and certain amino acids plus the combination of interrelated non-antagonistic items.

Albright (9) suggested an increased tissue breakdown with age caused by change in ratio between the catabolic corticosteroids and anabolic androgens and estrogens. There may be decreased plasma concentrations of several of the essential amino acids, hence leading to imbalances in necessary amino acids for patterned reparative responses. Any failure in timing in the assembly of the essential and lesser essential amino acids may mean a decrease in fabrication of tissue. Increased nitrogen excretion results from administration of cortisone. The three main constituents of plasma that must be built up by the blood-forming organs are albumin, globulin and fibrinogen (10) Plasma $-Fe^{59}$ globulin IV-7 or Cohn's fraction (11) is a protein. Integrity of the erythropoietic tissue of the body must be maintained by more than a large supply of iron (12). To live within the limits of one's abilities but operate on the level of their increasing capacities to use hematopoietic materials is part of the graded level of treatment begun in nutritional anemia. The complete program must be planned to help to retrain and readjust the total behavior of the blood building system of the whole human being. This is the object of the management. Normal human plasma contains 2.4 grams per liter of beta$_1$-globulin, capable of binding about 3 mg. of iron per 1000 cc.

Lyons and Mayerson (13) suggest a "deficiency of hemoglobin, among all the body proteins, is of particular surgical significance." Keys has suggested that twenty-four weeks on a semistarvation diet may lead to a hemoglobin deficit. "Recent studies have emphasized that serum iron is transported only when bound to a specific protein" (9). "The metal-combining protein is concentrated in Cohn's fraction IV-7 of the plasma and may be crystallized out as a beta$_1$-globulin which represents the plasma component capable of binding and transporting iron" (9).

The anti-pernicious anemia principle may be useful in overcoming nutritional anemia in some patients. "The hemoglobin level usually increases with that of the erythrocytes but may lag in some patients, owing to an insufficient supply of iron. This lag is readily corrected by the ingestion of therapeutic doses of iron" (10). First the type of iron must be chosen. Some clinicians have found ferric chloride and vitamin C administered simultaneously between meals in small divided doses helpful in combating the nutritional anemia of pregnancy. Ferrous sulfate has been in good standing in many circles. Sodium-iron-pyrophosphate is used for the iron enrichment of bread flours. Ferric pyrophosphate is used for the enrichment of rice.

In normal individuals iron equilibrium may be maintained with intakes as low as 5 milligrams daily. Women need 10-29 milligrams daily depending on their fertility, reproduction, menses and pathological states. Women need more iron than men. Infants and children take 0.6 to 2 mg. per kilogram. Infants up to one year take 1-2 milligrams per kilogram. A sick child would need more than the 0.6 mg./kilogram of the ordinary 4-8 year old. Infections increase the need for certain trace elements. Children do not need excess amounts of iron. Iron poisoning in infants has been reported. Protection is in some way connected with a normal protein intake and protein metabolism. Iron is absorbed chiefly in the first part of the duodenum. Normal iron resorption is gaged by several factors, and a normal intestinal wall does not let in excess iron. Apoferratin has about one quarter of its own weight in iron. When there is no free apoferratin then iron can be taken up. The relatively high pH in the duodenum can facilitate the formation of insoluble basic iron compounds. Resorption and absorption of iron is hampered by the absence of free HCl and of bile acid and achlorhydria should be treated. The administration of vitamin K is of value only when prothrombin is reduced as in poor liver function.

Absorption may be decreased in the presence of increased intestinal motility as in diarrhea and the coeliac syndrome. The normal individual absorbs iron in proportion to his need, the quantity absorbed being determined by the reserves of the element. The intestinal mucosa accepts or rejects the iron compounds. Anemic individuals absorb and utilize iron more efficiently as has been demonstrated repeatedly in late latent anemia of pregnancy. The HCl of the gastric juice converts the ferric compounds of foodstuffs into dispersed ferric ions.

Ferrin is a compound of ferric iron with apoferrin.

Ferrous iron is absorbed by the mucosal cells within which it exists in equilibrium with the ferric iron of protein complex. No more ferrous iron can be absorbed when the cells are physiologically saturated with this equilibrium mixture; ascorbic acid, cystine and the sulfhydryl groups of protein reduce ferric salts at pH5 or lower. Iron is absorbed in the ferrous form.

Up to this point protein deficiency is the chief finding in many of the iron-deficiency hypochromic anemias. Infection, hemorrhage, bleeding, deficient intake of iron and trace elements, vitamins, total calories and other nutritional factors, stress mechanisms, multiple births, congestive splenomegaly, and surgical intervention have been stressed as possible etiological causes of iron deficiency anemia. Scurvy may have an associated anemia. Rickets may have a deficiency of more than one mineral. Oral administration of iron may be fortified by a suitable dietary measure. Up to three months time must be allowed for the correction of the nutritional anemias. Treatment consists of suitable iron preparations, extra vitamins, high protein maintenance diet.

The nutritional whirl pool has protoprophyrin pigment, iron and stroma-globulin as the material of choice in protection against nutritional anemia. Features of the hematopoietic system are the bone marrow, reticuloendotheial system, spleen, liver, (liver extract not being the important inclusion here), and Intrinsic factor of Castle. The end result is the beta$_1$-globulin which has been crystallized from (16) fraction IV-7 of human plasma, and accounts for the capacity of the plasma to bind and transport iron. Microcytic hypochromic anemia may be due to loss of iron from bleeding. Twenty-five milligrams of iron are necessary for each rise of one percent in hemoglobin. The depression of the bone marrow by toxins and infections may be responsible for normocytic anemia. Anemia of the hyperchromic type has been described in Vitamin B_1 deficiency (17). Ferrous sulfate gives the most absorbable iron per weight of any of the numerous iron compounds. A study of American Red Cross Blood procurement records shows that (18) 12.6% of 73,783 women failed to meet a requirement of 12.3 gm. of hemoglobin per 100 cc. of blood, which was the minimum for acceptance of a person. Some authorities suggest the need for more careful evaluation of adolescent and teen age girls diets to provide for a better grade protein and larger inclusions of food iron. High caloric diets are more apt to be well balanced and can include some unexpected sources of iron as avocado, nectarines, loganberries, asparagus, beets, parsley, greens (chard, collards, dandelion, kale, mustard greens, spinach, turnip top) pecans, filberts, almonds, cooked legumes, as well as the better known whole grains and egg yolk. The availability of iron is high in molasses (19). Apricots, oatmeal and beef liver run high too. Lettuce, cabbage and raisins have more than twice as much as mutton, oysters and spinach.

Many anemic individuals overeat. Anemia superimposes a strain on previous eating habits, and those individuals with a trend toward obesity will be benefited by leaning on the proteins for limited calories instead of the highly diffusable carbohydrates. It is hard for obese anemic persons to realize that they will benefit from a reduced food intake. All awareness of the world is limited by the receptive range of functioning sense organs. It is their view that the only value of a diet lies in the attached discipline. A civil war veteran said he felt he should eat a green persimmon to shrink the stomach to fit the ration. "G. B. Shaw and G. K. Chesterton were great friends and greater opposites. Shaw was quietly sardonic, heretical, a lean vegetarian; Chesterton was loudly affirmative, orthodox and a heartily obese meat eater. Once, at a public dinner, Chesterton stared pointedly at Shaw's thin figure and remarked, "Looking at you, Shaw, people would think there was a famine in England." Turning to his rotund companion, Shaw observed, "And looking at you, Chesterton, people would think you were the cause of it." We must allow for individual differences and variations in people. The amount of heat given off by a resting man of average size is about equal to the heat of a 60 watt electric light or the flame of an alcohol lamp about 1 inch high.

For every gram of plasma protein reduced from normal there exists a 30 gram depletion of the tissue reserves. If serum proteins are needed they too must be built up to meet body needs by high levels, well timed, of suitable proteins with sufficient calories. The degree to which any nutritional deficiency crosses an altered pathway of utilization of a metabolite, determines the amount of nutritional awareness that must be applied to the topic.

Vitamin B_{12} is concerned in the development of the corpuscles; niacin and riboflavin are constituents of enzymes which are included in the functioning R.B.C.

Low phosphorus content of the diet has been found to produce larger iron stores, and excess calcium inhibits iron assimilation. Only ionic iron can be absorbed and ferrous iron is more readily absorbed than the trivalent forms in humans.

SUMMARY

One of the basic considerations in iron deficiency anemia is supplying adequate amounts of protein and iron. The function of the diet is to provide all of the nutritional materials simultaneously. Individual differences must be recognized in the daily recommended dietary allowance. Iron supplementation should be built on the premise that the food will carry some of the iron. For example, in pregnancy it will take 10 servings of iron containing foods to meet the daily normal iron need. The limits of the intestinal tract prevent the use of more than two pounds of fruits and vegetables a day. It would be impossible to meet the iron need in anemia by more food alone. Supplementary elemental iron should be offered either in the presence of ascorbic acid or some other acid, and not in the presence of high phosphorus content of diet or medications. If calcium or other alkaline materials must be given, they should be given separate from and not with the supplemental ferrous or ferric compounds.

CONCLUSION

1. Iron in food is present in varying amounts and in various degrees of availability.

2. Food cannot supply the necessary increment of supplemental elemental iron needed in hypochromic

iron deficiency anemia of nutritional origin, but must be augmented.

3. The etiological factors determine the time provided for the recovery.

REFERENCES

1. Block, R. J. and H. H. Mitchell: "The correlation of the Amino Acid Composition of Proteins with the Nutritive Value." Nutrition Abstracts and Reviews *16*, 249, 1946.
2. S. A. Levinson and R. P. Macfate: *Clinical Laboratory Diagnosis.* Lea and Febiger: Philadelphia, 1951.
3. R. M. Leverton, G. Clark, P. M. Bancroft, E. Copeman: Further Studies of the Use of Meat in the Diet of Infants and Young Children," The Journal of Pediatrics *40*, 6, 761-766 (June) 1952.
4. Editorial, J. A. M. A.: The Functions of Ferritin, *150*, 1, 36-37, (Sept. 6) 1952.
5. C. H. Smith, I. Shulman and J. E. Morgenthau: Serum Iron and Iron-Binding Protein, *Advance in Pediatrics* V. pp. 195-227, 1952.
6. May, C. D., et al: Am. J. Dig. Dis., *82*:282-309, 1951.
7. The Functions of Ferritin: Editorials and Comments, The Journal of the American Medical Association, *150*, 1, pp. 36-37, Sept. 6, 1952.
8. Henry A. Lardy: *Respiratory Enzymes*, Burgess Publishing Co., 426 So. Sixth St. Minneapolis, Minn. p. 102.
9. F. Albright: Ann. Int. Med. *27*:861, 1947.
10. Lab. Investigations I:1-18, 1952.
11. J. Cl. Invest. 30 (12 pt. II) 1512-1526, 1951.
12. J. Cl. Invest. 31:(1) 32-39, 1952.
13. Champ Lysons, M.D. and H. S. Mayerson, Ph.D.: "The Surgical Significance of Hemoglobin Deficiency in Protein Depletion," Journal of the American Medical Association, *135*:km 9-11, Sept. 6, 1947.
14. C. H. Smith, I. Shulman and J. E. Morgentau, "Serum Iron and Iron-Binding-Protein." *Advances in Pediatrics:5*, pp. 195-227, 1952.
15. Murphy, W. P.: Twenty-Five Years' Experience in Treatment and Management of Pernicious Anemia: The J. A. M. A., Vol. 149, No. 10, pp. 907-912, July 5, 1952.
16. Frances A. Johnston: "New Developments in the Theory of Iron Metabolism" Journal of the American Dietetic Association, Sept. 1951, pp. 739-744.
17. C. A. Elvehjem: "The B Vitamin Complex" Journal of the American Medical Association *138*:13, pp. 960-971, Nov. 27, 1948.
18. G. W. Hervey and R. T. McIntire, and V. Watson: "Low Hemoglobin Levels in Women Are Revealed by Blood Donor Records": Journal of the American Medical Association 149:12, 1127-1128, July 19, 1952.
19. Am. J. Dig. Dis. Vol. 6, No. 7 (Sept.) 1939 pp. 459-62.

EDITORIAL

A PRACTICAL REDUCING REGIMEN

A. W. Pennington* of Wilmington, Delaware, states that the most practical reducing regimen in his experience is as follows—(1) Walk one-half hour before breakfast, (2) At each of the three meals of the day eat 6 ounces of lean meat and two ounces of fat, cooked weight, *or more,* in that proportion. Do not add salt and do not use salted meats, (3) Along with the meat have an "ordinary sized" portion of one of the less concentrated carbohydrate foods and a cup of black coffee or tea, (4) Drink water in liberal amounts. He states that most obese persons lose about 7 pounds a month on this regimen. If the carbohydrate is omitted, and nine ounces of lean meat with 3 ounces of fat at each meal is used, the loss per month is usually 12 pounds.

Obesity, according to Pennington, is due to an inability to oxidize carbohydrate. Restriction of carbohydrate removes the inhibiting effect of pyruvic acid on the utilization of fat. The mild ketosis, which develops, spares protein. Such a diet is said to be found associated with a remarkably low incidence of cardiovascular-renal disease in a large group of people.

Naturally everyone is delighted to have what sounds like a simple plan for weight reduction. It goes without saying that the regimen of Pennington ought to be tried out very extensively by all internists.

D. M. Hegsted of Boston, in discussing Pennington's paper, feels that we should be skeptical of all methods of weight reduction until they have been rigidly compared under various circumstances. Hegsted feels that possibly Pennington is a better psychologist than he thinks and that similar results might not be obtained by everyone. At all events, while not doubting Pennington's results, Hegsted does not accept his explanation of those results. Pennington, in rebuttal, states that his conceptions seem to explain one of the phenomena of adiposity better than does the "simple overfeeding" concept.

We have here all the makings for a new controversy. Let us hope that from this controversy some real progress in the treatment of adiposity will soon result. For the moment, Pennington's work is the center of interest.

*Pennington, W. A.: Practical Reducing Regimens. Overeating, Overweight and Obesity. The National Vitamin Foundation, Inc., 150 Broadway, New York 38, N. Y. 1953.

BOOK REVIEW

THERAPEUTIC NUTRITION. Herbert Pollack and Seymour L. Halpern, with the collaboration of the Committee on Therapeutic Nutrition of the Food and Nutrition Board, National Research Council. Publication 234, National Academy of Sciences, National Research Council, Washington, D. C., 1952.

A treatise on therapeutic nutrition will give evidence of restraint in direct proportion to the erudition of its authors. The present volume says, in effect,—be sure to feed well those who are ill or have been severely injured,—then proceeds to many details and to specific exceptions, using what knowledge we have. It is certainly true that little attention has been paid by the medical schools to the nutritional aspects of therapeutics. The subject is of major importance in acute conditions, but it is also of great urgency in chronic disease. The current tendency is definitely away from restricted diets and emphasis is correctly placed upon the importance of liberal and well-selected feedings. We recall a physician who gained for himself a fine practice by the simple expedient of permitting his patients something to eat, in a community where formerly the emphasis had been on restriction in almost all diseases and conditions.

Metabolism in relation to food intake, to hormones, vitamins and minerals is ably and succinctly presented with as much emphasis on what we do *not* know as upon what has been proved. Clinical methods of evaluating the nutritional status of the patient are particularly helpful. In the dietary deficiencies it is well stated that we do not, in America, often see single vitamin deficiencies. In every case, therapy usually demands the use of a multiple vitamin preparation with emphasis on the B-complex in cases of injury, trauma, fracture and surgical operations. Potassium, even when required, must be administered with caution.

The body is a vast pool of chemical activity in which enzymes, vitamins, hormones, minerals and trinary foods work together in the most complicated manner imaginable. The peculiar catabolic effects of trauma (in its broadest connotation) involving, as they do, the pituitary-adrenal system, receive special attention, parallel, to some degree, with the concepts of Selye, especially his "alarm reaction."

Fevers must no longer be starved. The recommended dietary allowances for normal individuals are quite inadequate following trauma and stress, and may need to be increased ten-fold. Protein of good quality is essential and this practically means animal protein. Excessive reduction of fat in liver disease is not recommended. Lipotropic substances are unnecessary if a "normal" diet can be consumed. The intravenous administration of vitamins is deprecated because of their rapid excretion, the intramuscular route being preferred.

Every physician should obtain a copy of this book. Today the experts demand that patients eat. Restricted diets are used only when very necessary. Meat looms greater than ever as perhaps our best single food. The ideas of the vegetarians do not stand up in the face of what we know scientifically. Nevertheless, we as physicians have seen many things which shout defiance to some of the modern concepts of scientific nutrition. Possibly this complicated metabolic mass, known as the human body, is even more versatile than its students. Under some circumstances, at least, it can do things quite unexpectedly and without following an erudite routine. That is why the authors of this book so refreshingly admit ignorance, and why, also, we physicians often "get by" when strictly speaking, we ought to fail.

GENERAL ABSTRACTS OF CURRENT LITERATURE

GAY, B. B.: *Esophageal perforations: a review of etiology with representative case presentations.* Am. J. Roentgen., Rad. Ther. & Nuclear Med., 68, 2, August 952, 183-197.

There are many causes of acquired perforation of the esophagus: a normal esophagus may perforate due to increased intraesophageal pressure. There may be instrinsic and extrinsic injuries, or cancer, inflammation or peptic ulcer or diverticulitis. Severe substernal pain referred to the back, and shock, are the chief symptoms, and the condition may be confused with cholecystitis, pancreatitis, intestinal obstruction, perforated appendix, pulmonary or coronary infarction, spontaneous pneumothorax, acute pleural effusion and dissecting aneurysm. Subcutaneous emphysema in the neck is an important symptom. Free air under the diaphragm rules out esophageal perforation. Diagnosis is made by chest films following barium swallow, which may reveal a fistulous tract leading into the trachea. Hydropneumothorax, chiefly on the left side, is characteristic of low perforation. A negative esophagram should not exclude the possibility of perforation if characteristic symptoms are present.

DUNLAP, R. W., HALLENBECK, G. A. AND HANLON, D. G.: *Portal hypertension associated with sarcoidosis and with hemachromatosis: report of 2 cases with splenectomy and splenorenal anastomosis.* Proc. Staff Meet. Mayo Clin., July 2, 1952, 266-272.

Two cases of portal hypertension are described. One was a pregnant woman, in whom the portal hypertension was associated with sarcoidosis of the liver

and spleen. The other case was a man in whom portal hypertension was associated with hemachromatosis. In both cases splenectomy was done, also splenorenal anastomosis. Both made uneventful recoveries. The woman gave birth to a baby five and a half months after the operation, without complications. The authors emphasize the importance of needle biopsy of the liver in selected cases as an aid in the accurate diagnosis of liver disease.

MILLER, A. A.: *Human salmonella typhi murium infection due to duck eggs, with special reference to flocks of ducks.* Brit. Med. J., July 19, 1952, 125-127.

Miller reports investigations following two severe and two fatal cases of Salm. typhi murium infection attributable to the eating of duck eggs. In 2 cases the incriminated eggs were successfully traced to two flocks of ducks. The flock to which the third egg was traced was the probable source. In the first infection the same V. phage type of Salm. typhi murium was isolated from 2 out of 9 eggs laid by six ducks, and from the ovary of one duck, from the intestinal tract of a second duck, and from both organs in a third duck. Agglutinating titers showed that 5 out of 6 ducks were positive reactors. In the second investigation Salm. typhi murium V_1 phage Type 4 was isolated from the patient, from the farmer and his sister, and from the one cloacal swab obtained from the flock of ducks to which the suspected egg was traced. Practically all the ducks in this flock were positive reactors.

CUNNINGHAM, J. A. K.: *Subacute and chronic hepatitis.* New Zealand Med. J., LI, 282, April 1952, 69-74.

Cunningham analyzes 37 cases of subacute and chronic hepatitis, showing the tendency of the disease to progress to biliary cirrhosis or nodular cirrhosis. In only one case was faulty nutrition the obvious etiological factor. Alcoholism was responsible in 6 cases. Infective hepatitis seemed to be the cause of cirrhosis in 13 cases. In 17 cases no cause was found. Although infective hepatitis is uncommon in older women in New Zealand, such patients run a serious risk of developing chronic liver disease. Why these older women are unduly susceptible is unknown, but endocrine factors are under suspicion.

KITAMURA, H.: *A new estimation method of furoylglycine, and furoic acid as an indicator of liver function test.* Kyushu Memoirs of Med. Sci., 1, 1, June 1950, 7-14.

Furoic acid may be used for a liver function test by the estimation of furoylglycine, using a new color reaction. After the addition of bromine water in slight excess to a dilute furoylglycine solution (as obtained from blood or urine), and the removal of the yellow color by aeration or thiosulfate, the solution is made alkaline with concentrated ammonium carbonate solution, and a pretty violet color immediately develops. Clinical and experimental evidence for the usefulness of the test is presented.

JACOBSON, G., CARTER, R. A. AND SNYDER, E. N.: *Intussusception (colocolic) with spontaneous extrusion of the intussusceptum.* Am. J. Roentgen., Rad. Ther. and Nuclear Med., 68, 2, August 1952, 198-203.

A case of colocolic intussusception followed by spontaneous extrusion of a gangrenous intussusceptum, 23 inches of descending colon, and recovery, is reported. This was complicated by (a) thrombosis of the inferior vena cava which later recanalized, (b) progressive stricture and spontaneous ileosigmoidostomy at the site of auto-anastomosis.

An unusual x-ray manifestation of intussusception is described. When a patent intussusceptum advances into a relatively fixed intussuscipiens, i.e., descending colon into sigmoid colon, examination by barium enema may reveal a continuous column of barium with changes simulating cancer, bowel perforation and abscess formation.

STEVENSON, J. S.: *Further observations on the occurrence of Bact. Coli D433 in adult feces.* Brit. Med. J., July 19, 1952, 123-124.

Stevenson found that Bact. Coli D433 (the alpha-type of Giles and Sangster) can be isolated from about 1 in 200 adult hospital patients in Glasgow. Up to 10 percent of mothers of infected babies may also harbor this organism. The normal adult, however, does not become infected during contact with infants suffering from diarrhea and vomiting associated with the specific coliform organism. Stevenson in 1950 reported 14 cases of diarrhea in adults associated with this organism, but no explanation for this outbreak has been found.

HSIA, D. Y. AND GELLIS, S. S.: *Hepatic dysfunction in infectious mononucleosis in children.* Am. J. Dis. Child., 84, 2, Aug. 1952, 175-183.

In 62 children with a presumptive diagnosis of infectious mononucleosis, 84 percent with a heterophile titer of 1:56 or higher showed positive results of liver function tests. Those cases showing no abormalities of liver function were later proved not to have had infectious mononucleosis. In children, liver function tests should be used as an addition to the diagnostic methods used for infectious mononucleosis. Since flocculation persisted in 4 to 12 children with the disease for considerable periods, and in view of the pathological similarity between infectious mononucleosis and infectious hepatitis, it would now appear advisable to treat such children as if they had diffuse hepatitis.

FRANKLIN, A. W. *and* HOSFORD, J. P.: *Meconium peritonitis due to a hole in the fetal intestinal wall and without obstruction.* Brit. Med. J., Aug. 2, 1952, 257-259.

Two cases of infants are reported in whom peritonitis due to the escape of aseptic meconium developed a few hours after birth. Both cases were successfully operated on, the "hole" found and closed and recovery occurred through the use of fluids and antibiotics. There was no way to explain the occurrence of the "holes," and no theories are advanced. The chief difficulty was in finding the holes because of intense matting of the bowels and peritoneum. Should another similar case occur, the authors propose to fill the peritoneal cavity with saline, and then bubble oxygen through the bowel, hoping to detect the point of leakage as one does in a punctured automobile tire.

GRUNBERG, A., BLAIR, J. L. AND ST. HILL, C. A.: *Congestive splenomegaly due to pancreatic cystadenoma.* Brit. Med. J., Aug. 2, 1952, 265-266.

The case is presented of a middle-aged woman whose anemia was due to bleeding from the gastrointestinal tract, and who presented an unexplainable splenomegaly. For some time blood transfusions and conservative treatment were used. No radiological evidence of peptic ulcer could be found. Finally the abdomen was explored and a large cystadenoma of the body and tail of the pancreas was found compressing the splenic vein. The spleen, the tumor and part of the pancreas was removed with resultant cure of the disease, the tumor being benign. For a time, a lowered glucose tolerance was present, but eventually the carbohydrate metabolism returned to normal. Surgical intervention should be considered in all cases of congestive splenomegaly since, as in this case, a tumor may be the underlying cause.

PATTERSON, H. S.: *Abdominal pain in childhood.* Med. J. Australia, July 26, 1952, 115-116.

Simple abdominal colic of infancy is explained by the author by the feeding habits. In one type of case the baby feeds too fast and in another he gets too little food because of faulty nipples. He recommends sodium bicarbonate Gr. II, glycerine M. II, spiritus ammonii comp. M. II and aqua anethi ad 1 dram. In chronic indigestion with cyclic vomiting in children from 5 to 12 years of age, he finds the basis of the trouble in stress within the home, in faulty diet, in fat indigestion and finally in gastrointestinal allergy. He recommends soda bicarbonate Gr. V, dextrose Gr. X and chloroform water to 1 dram, given after meals. If necessary 5 drops of belladonna in 1 dram of the elix. of benadryl may be given, especially where allergy is suspected.

SHEHADI, W. H.: *Telepaque.* Am. J. Roentgen., Rad. Ther. and Nuclear Med., 68, 3, Sept. 1952, 360-368.

Telepaque is a new compound which seems to satisfy the requirements of an ideal cholecystographic medium better than any of the media now in use, and is therefore considered superior. There is a decidedly low level of side reactions. It is readily absorbed and the gallbladder responds promptly to the fat meal. There is greater density and improved visualization of the gallbladder. The frequent visualization of the bile ducts opens up a new field in the study of the biliary tract. Possibly a slightly smaller dose than the presently recommended 6 tablets may be found sufficient for normal sized individuals.

O'SULLIVAN, J.: *The management of peptic ulceration.* Med. J. Australia, Jan. 17, 1953, 59-61.

O'Sullivan deals with the radiological aspects of peptic ulceration and devotes a considerable portion of his paper to esophageal ulcer and to ulcer occurring in a stomach which has slid into a hiatus hernia of the diaphragm. In cases of massive hemorrhage, in desperate cases and with patients who are unable to cooperate, O'Sullivan finds that the use of the barium meal is unfortunately not very informative. (This has not necessarily been the experience of Hampton and others in the U. S. A.-reviewer.)

KAHN, A.: *Treatment of liver failure.* J. Arkansas Med. Soc., XLIX, 10, March 1953.

In a review article, Kahn emphasizes the importance of a high protein, high carbohydrate and moderate fat diet in treating the diseased liver. Meat is considered the best source of protein. About 300 grams of sugar per day is advisable. The use of choline and methionine permit the use of moderate amounts of fat in the diet, 130 gms. daily being now permitted. Alcohol should be withheld in cases of hepatic decompensation. Reduction of the sodium in the diet aids in the control of ascites. Vitamin K, parenterally, is advisable where the prothrombin time is low. Cortisone has not as yet found a proven place in treating these cases.

KURTZ, L. D.: *Foreign bodies in the gastro-intestinal tract.* Alex. Blain Hosp. Bull., 11, 4, Nov. 1952, 83-86.

When a foreign body is swallowed, it normally requires 1 to 15 days to pass through the gastrointestinal tract. If such body has not entered the stomach, endoscopy is the best method of removal. Once it has entered the stomach, the best policy is watchful waiting. Rounded or oval bodies almost invariably pass through uneventfully. If the object is too large there may be delay at the pylorus. If the object is long, delay may occur either in the stomach or duodenum. Usually, 5 days should be the limit of the waiting period. A case is reported in which 19 days elapsed without incident prior to the operation. In this case, in a child, a bobby pin would not pass the duodeno-jejunal juncture.

BURT, L. I: *The management of late acute appendicitis.* Med. J. Australia, Nov. 29, 1952, 773-774.

Burt recommends that patients in whom the evidence for localization is not clear should be operated upon as soon as possible but when there is clear evidence of localization in the form of a mass and absence of generalized peritonitis, the patient is better not operated upon, for, in spite of available antibiotics, careful watching is required. If an appendiceal mass has subsided readily without drainage, the patient should wait three weeks after leaving hospital for the date of appendicectomy. When surgical drainage has been performed, three weeks after all discharge has ceased is the minimum time to elapse before operation.

KIRSHEN, N. M.: *Pathophysiology of jaundice.* Illinois Med. J., 103, 1, Jan. 1953, 45-47.

The factors producing jaundice may operate *before*, *in*, or *behind* the liver cells, but such factors usually operate in pure form for only a brief time. Anemia in hemolysis, back pressure in obstructive jaundice, and toxemia in hepatitis may change the characteristics of the primary mechanism very quickly. A careful history of possible contact with a hepatotoxic agent is needed. Repeated studies of the bilirubin in blood and urine, and of urobilinogen in the urine and stool, a critical evaluation of liver function tests and, occasionally, a liver biopsy, will help us to make a correct diagnosis in about 80 percent of the cases of jaundice.

TREATMENT OF URINARY TRACT INFECTIONS WITH FURADANTIN

Significantly good results with the new drug, Furadantin (nitrofurantoin, Eaton), in the treatment of chronic urinary tract infections that were unresponsive to other modern antibacterial agents are reported by Sidney Mintzer, Elmer R. Kadison, William H. Shlaes and Oscar Felsenfeld in *Antibiotics and Chemotherapy* (3:151-157 (Feb.) 1953). This new antibacterial nitrofuran has been tailored specifically for the treatment of urinary tract infections. It is the first nitrofuran designed for systemic administration.

Furadantin, with its broad spectrum of activity, "offers much promise for the treatment of bacterial urinary tract infections," the authors state. No untoward side effects such as proctitis, pruritus, abdominal pain, diarrhea, crystalluria or sensitization, were noted among 79 cases. A few patients exhibited nausea or emesis, the number being 2 out of 59 on the present dosage level.

These clinical and laboratory studies, at the Hektoen Institute for Medical Research, Cook County Hospital, Chicago, were among those which preceded the recent release of Furadantin for general use by physicians. Of 12 refractory cases, 5 were cured completely and 3 markedly improved. Among 25 patients with cystitis or pyelonephritis, 13 were clinically and bacteriologically cured after 3 days, 4 were improved, 3 were failures and therapy was terminated in 5 after nausea from dosage now known to be excessive. Bacteria eliminated included Proteus sp., Pseudomonas sp., A. aerogenes and E. coli.

Mintzer et al. report that about 45 percent of the Furadantin administered orally is excreted in the urine, with blood levels at any time remaining extremely low.

Antibiotics and sulfonamides are far from solving the problem of bacterial urinary tract infections, in the light of the development of bacterial resistance and other factors, the authors comment. For this reason they welcomed the opportunity of studying a new antibacterial nitrofuran, since this group of drugs shows "little tendency to permit development of bacterial resistance."

In clinical tests of Furadantin at the Bowman Gray School of Medicine, Wake Forest College, Winston-Salem, N. C., 36 organisms were eradicated from the genitourinary tract, including 16 of 22 strains of E. coli, 4 of 6 strains of A. aerogenes, 3 of 5 strains of Proteus sp. and 1 of 3 strains of Pseudomonas aeruginosa.

The results were reported by Charles M. Norfleet, Parker R. Beamer and Harry M. Carpenter at the Southeastern Section, American Urological Association, Boca Raton, Fla., April, 1952. Of 33 patients with acute or chronic pyelonephritis or cystitis, 17 were cured clinically and bacteriologically, 14 were improved and 2 were failures. "Furadantin is an effective broad-spectrum chemotherapeutic agent and we have found it to give gratifying results," the investigators said.

At Maimonides Hospital, Brooklyn, and the State University of New York College of Medicine, Charles E. Friedgood and Anthony Danza administered Furadantin orally to 22 patients with Proteus infections of the urinary tract that had proved refractory to intensive antibiotic therapy. Clinical and laboratory cures were achieved in 14 cases and symptomatic cures in 8, with no failures. The results were reported to the American College of Surgeons Clinical Congress in New York in September, 1952. Subsequently Friedgood told the Brooklyn Urological Society that similar therapy had produced excellent results in 80 cases of stubborn urinary tract infections.

TREATMENT OF URINARY TRACT INFECTIONS WITH A NEW ANTIBACTERIAL NITROFURAN

Preliminary studies of the new nitrofuran, Furadantin, brand of nitrofurantoin, proved it to have a broad spectrum of antibacterial and antiprotozoal activity *in vitro* and in animal experiments.

It is effective against many gram-negative and gram-positive bacteria *in vitro* and *in vivo*, especially against those common to urinary tract infections. It retains effectiveness in the presence of various organic substances and shows no tendency to permit development of resistant bacterial strains *in vitro*. It is not effective against rickettsiae, viruses or fungi *in vitro*, but did demonstrate effectiveness against certain protozoa both *in vitro* and *in vivo*. The drug does not lower appreciably the fecal bacterial count, suggesting that no overgrowth of fecal fungi is to be expected during therapy. *In vitro*, synergism occurs between Furadantin and penicillin and streptomycin.

Animal and human studies reveal that it appears to have low toxicity at clinical dosage levels. Untoward side effects during treatment were minimal; a few patients exhibited nausea or emesis, but there was no proctitis, pruritus, abdominal pain, diarrhea nor crystalluria. No sensitization occurred in over 70 patients.

Furadantin, at the dosage level finally chosen, was administered to 12 patients with chronic urinary tract infections, who had previously been treated unsuccessfully with other modern antibacterial agents. It is considered significant that good results were obtained in 8 of these.

It appears that this drug offers much promise for the treatment of bacterial urinary tract infections.

PARKE-DAVIS OFFICIAL CITES ADVANCES IN TREATMENT OF MALARIA, AMEBIC DYSENTERY

Dr. H. E. Carnes of Parke, Davis & Company said recently the development of drugs for the treatment of malaria and amebic dysentery are "approaching a stage never before enjoyed by mankind."

Dr. Carnes, of the pharmaceutical firm's clinical investigation department, spoke on "Antimalarials and Amebacides" at the meeting of the Southeastern Society of Hospital Pharmacists in the Jung Hotel.

He recalled that man has continually fought malaria and amebic infestations since the beginning of time.

"Efforts to control malaria and amebic dysentery have been aimed at environmental and sanitary control, and also at drugs for treatment and suppression of the parasites in man," he said.

Dr. Carnes, whose department conducts field tests of newly-discovered drugs and medicinals, reported that "advances in development of drugs which are safe, convenient,

and effective in treatment and suppression of these diseases are approaching a stage never before enjoyed by mankind."

WINTHROP'S NEW RADIOPAQUE OFFERED IN NEW PACKING

Hospitals and other large users of the new radiopaque compound Telepaque may now obtain the product, which is supplied in 0.5 Gm. tablets, in bottles of 500, it was announced by Winthrop-Stearns, Inc.

The new bulk size is packed in a carton containing, in addition to the bottle of 500 tablets, one hundred printed envelopes for use in dispensing the tablets to patients.

Due to its greater iodine content, Telepaque has been cited in medical literature as a superior cholecystographic medium for visualizing the gallbladder and biliary ducts.

SURDON RELIEVES PREMENSTRUAL TENSION AND DYSMENORRHEA

Surdon, a new, "triple-prescription" tablet recently introduced by Organon Inc., of Orange, N. J., helps to control the symptoms of premenstrual tension and dysmenorrhea. Each Surdon tablet contains 5 mg of Progestoral (Organon's brand of ethisterone, the orally effective corpus luteal hormone), 15 mg of thiamine hydrochloride, and 15 mg of phenobarbital.

Each of the three Surdon ingredients is included for its tested and proven action in the treatment of patients suffering from dysmenorrhea or premenstrual tension. Progestoral is provided for its uterine relaxant and hormonal balancing actions. Thiamine hydrochloride aids the liver to inactivate excessive estrogen which is frequently the cause of symptoms, in addition to providing an oft-needed boost. Phenobarbital allays apprehension, tension and pain—symptoms from which premenstrual tension and dysmenorrheic patients most frequently seek relief.

Surdon tablets are recommended in an average dose of one or two per day during the last seven to ten days of the menstrual cycle. This usually suffices to control the symptoms of either premenstrual tension or dysmenorrhea.

Surdon tablets are available for physicians' prescriptions in boxes of 30 tablets, sanitaped for greater dispensing and patient convenience. As with all Organon products, Surdon is never advertised to the laity. Descriptive literature on Surdon is available on request.

RESPONSIBILITY OF PATIENT IN SEEKING EARLY MEDICAL CARE TO BE EMPHASIZED IN NEW SERIES OF MAGAZINE ADS

Detroit.—Parke, Davis & Company announced recently a new series of advertisements will be addressed to the general public, starting this month, on the importance of prompt and proper medical care.

Ralph G. Sickels, director of advertising and public relations for the pharmaceutical firm, explained the central theme will be:

"In the hands of your physician, you're in good hands."

The advertisements, he added, will emphasize that medical science has a vast store of new knowledge, and that this knowledge is constantly increasing through world-wide research.

Medicine's Greatest Problem: Neglect and Delay

Although Parke-Davis has been stressing the "See Your Doctor" theme in its national advertising for 25 years, the new series will present "copy and layout which we think are not only different, but unusually fresh, provocative and effective," Sickels said.

Neglect and delay in seeking the physician's help are viewed by many as "the greatest problem facing medical science today," he pointed out. The problem may assume even greater significance with the rising incidence of the degenerative diseases.

"We believe it is part of our responsibility, as a maker of medicines, to reason these people away from the tragic pitfalls of neglect and delay," he said.

Four advertisements already have been prepared and scheduled.

The first dramatically shows a man who will "speak to no doctor," "see no doctor" and "hear no doctor." The copy emphasizes that such a man is his own worst enemy.

"Your own doctor has at his disposal all of the discoveries, all of the knowledge, of modern medical science," the advertisement says. "But you are the only one who can put these vast resources to work to help you."

The advertisement appeared in The Saturday Evening Post April 25 and This Week Magazine May 17.

Heart Disease and Cancer Are Other Subjects

The second, "Ever See a Telegram from Your Heart?" points out that "by taking advantage of the help your doctor can give you now, you increase your chances of living a good life with a bad heart." It is scheduled to appear in Saturday Evening Post May 16; Time, May 25; Newsweek, June 8; This Week, June 21; Woman's Home Companion, June; and Good Housekeeping, July.

"Is the secret of cancer locked in this cell?" is the headline of the third advertisement. It explains that doctors today are saving about one in four cancer patients and refers to an American Society estimate that the cure rate could be increased to two in four—without further knowledge — if patients would report symptoms in time to receive prompt, thorough treatment. This ad is scheduled for Life, June 15; Collier's, July 4; Woman's Home Companion, August; Good Housekeeping, September.

The fourth also has to do with heart disease. Under the headline, "Do You Know This Man?" it points out that negligence causes thousands of deaths. The ad is slated for publication in Life, July 13; Time, July 20; Newsweek, Aug. 3, and Collier's, Aug. 8.

Other advertisements will appear in 1953, all with the theme, "In the hands of your physician, you're in *good* hands."

Parke-Davis told the medical profession about the new advertising in a double-page announcement which appeared in the April 18 issue of the Journal of the American Medical Association. Similar announcements will be in state medical journals during May.

Carefully Written to Avoid Raising False Hopes

Sickels said the advertisements have been carefully written to avoid the possibility of stimulating hypochondria and encouraging self-diagnosis.

"Equally important," he added, "the advertisements keep away from statements that might cause undue optimism or raise false hopes."

SINUSITIS

Two Pittsburgh physicians reported recently for the first time the clinical use of a new drug in the treatment of acute and chronic sinusitis and infectious and allergic rhinitis.

The report came from Drs. Sidney N. Busis and Louis L. Friedman of the Departments of Otolaryngology of the University of Pittsburgh Medical School and Montefiore Hospital, Pittsburgh, Pa. They identified the new drug as Biomydrin, a nasal spray which rendered the nasal mucosa sterile in a number of cases of sinusitis. Biomydrin is available only on doctor's prescription.

(In Yonkers, N. Y., research scientists of Nepera Chemical Company, where Biomydrin was developed, said that the unusual therapeutic action of Biomydrin is due to a new antibacterial agent, thonzonium bromide, developed as a result of work done at the research laboratories of Nepera.)

The investigating doctors reported the new nasal medication's distinct, significant factor was that it produced sterile cultures taken from nasal passages in some cases only one day after the drug was administered.

Drs. Busis and Friedman, making their report in the scientific journal Antibiotics and Chemotherapy, said that Biomydrin had been administered to 95 unselected patients of varying ages and that 65 patients were observed through full treatment.

"Biomydrin contains the time-tested phenylephrine hydrochloride to produce rapid and effective vasoconstriction without rebound congestion," the doctors said. "It supplies thonzylamine hydrochloride, an antihistaminic of proven potency and infrequent side reactions, to augment the decongesting effect of phenylephrine, as well as to aid in the control of local allergic manifestations. It combines neomycin and gramicidin to provide a potent chemotherapeutic effect against a wide spectrum of all common gram positive as well as gram negative bacteria.

"Neomycin is active not only against a wide variety of both gram positive and gram negative organisms, but is said to be the only antibiotic effective against strains of both *Proteus* and *Pseudomonas*, a point of considerable import in view of the tendency of these organisms to emerge as dominant strains in the nasopharynx of patients undergoing treatment with the common antibiotics."

(The value of gramicidin and neomycin as used in Biomydrin is that they are almost never used systemically and consequently do not deny to the patient the subsequent use of effective agents for the treatment of serious systemic infections.)

According to research scientists of Nepera Chemical Company, the new wetting agent, thonzonium bromide, "is not only itself a highly active bactericidal drug against a broad spectrum of organisms, but also potentiates the antibiotic activity of the neomycin-gramicidin mixture in a truly synergistic manner."

In reporting on the therapeutic action of Biomydrin, Drs. Busis and Friedman said, "The results of the treatment were evaluated in every instance by the patient's own report on his subjective symptoms as well as by our own objective findings on subsequent examination, as determined by the degree of redness and swelling of the turbinates and nasal mucosa, and the amount of purulent secretion in the nose and nasopharynx. To evaluate the shrinking action of the drug, patients were observed for at least one hour after packing.

"There was no instance of precipitation of nasal obstruction requiring more and more frequent use of the spray to give relief. Our own examinations offered objective demonstration of prompt decongestion with no evidence of rebound congestion. In almost all of the patients, our own examinations showed improvement, as determined by a progressive decrease in the signs of inflammation and the decrease and disappearance of purulent secretion."

Smears and cultures were obtained from 18 patients treated with Biomydrin during the course of treatment. Specimens were secured before treatment was given by the doctors and at least several hours following the last application of Biomydrin.

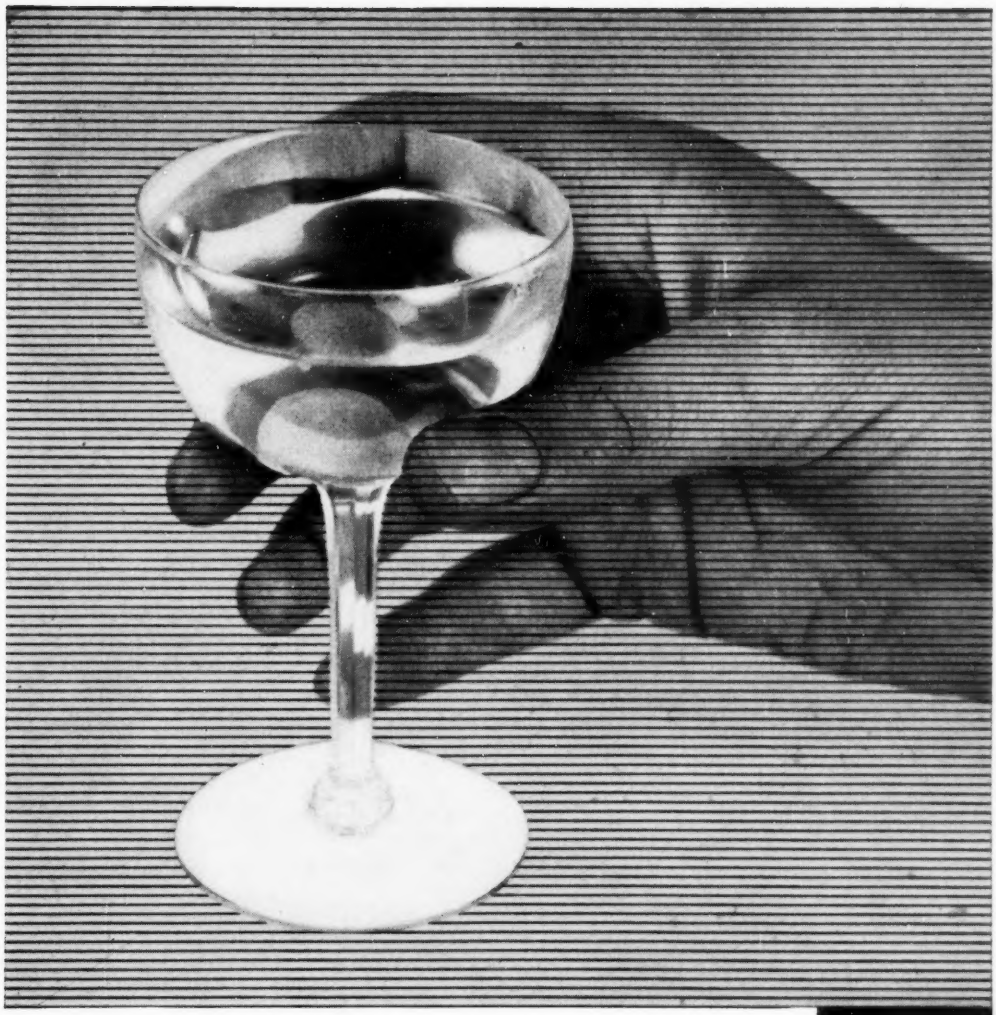
"In 13 instances no growth at all was obtained from the first post-treatment culture. In 9 of these patients, the negative cultures were obtained during the first repeat visit which occurred after only one day of treatment; in another seen for the first time after two days and, in two others, re-examined for the first time after six and seven days respectively," the doctors said.

Bacteria were cultivated from the five remaining patients after treatment with Biomydrin, but it was either impossible to culture the organisms present before the treatment, or to isolate them, and in two cases where organisms persisted, a "marked reduction in the number of colonies in the repeat cultures was indicated.

"That the above described effects of Biomydrin on the clinical courses and bacteriologic findings are real and not coincidental was demonstrated by the results obtained from eight patients who were subjected to the same procedures in every instance, with the exception that the solution packed or sprayed in the nose consisted only of normal saline packaged in similar containers. These patients showed no benefit either subjectively or objectively. The bacteriologic and cytologic findings in these patients, as expected, reveal no consistent effect of the type that resulted from the use of Biomydrin," the doctors stated.

"Under the conditions of use described in this report, intranasal medication with Biomydrin provided satisfactory clinical and bacteriologic response in this limited series of cases," doctors Busis and Friedman said. "Our preliminary results seem very promising and warrant further investigation."

In evaluating Biomydrin as a topical treatment for nasal infections, Drs. Busis and Friedman said:



Once the damage is done
High-potency lipotropic therapy is important

When prolonged dietary indiscretion results in liver damage and related disturbances, high-potency lipotropic therapy is indicated. WYCHOL furnishes this.

Palatability unusual in a preparation of this type simplifies the problem of keeping patients on WYCHOL therapy.

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CHOLINE AND INOSITOL

Bottles of 1 pint.

Also available: Capsules WYCHOL, for supplementary therapy.

Wyeth

Philadelphia 2, Pa.

for the patient
who needs to
simmer down—

Gentle

SEDAMYL
Trademark
[ACETYLBROMDIETHYLACETYLCARBAMID SCHENLEY]

Not a Barbiturate

provides ideal **daytime** sedation
without hypnosis

SEDAMYL* quickly relieves the nervous tension and anxiety so often generated by the strains of modern life.[1,2] In 333 patients suffering from nervousness, anxiety, and related psychosomatic complaints, SEDAMYL proved effective for daytime use in 90 percent of cases.[1] Tubes of 20, bottles of 100 or 1000 tablets.

1. Tebrock, H. E.: M. Times 79:760, 1951.
2. Geyer, H. W.: Delaware M. J. 23:255, 1951.

SCHENLEY LABORATORIES, INC.
LAWRENCEBURG, INDIANA

schenley

*Trademark of Schenley Laboratories, Inc.
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"It produces prompt, lasting shrinkage of the nasal mucosa without secondary congestion.

"There has been no evidence of significant local or systemic undesirable effects with the exception of an occasional patient who complained of transient stinging.

"It is effective as an antibiotic in clearing the nose of pathogenic organisms and purulent secretions. In many cases, sterile cultures were obtained after a brief period of treatment.

"Direct smears for cytology indicate that there is a definite decrease in polymorphonuclear neutrophils and eosinophils after a course of treatment.

"In vitro, it inhibited all growth of all organisms cultured.

"It has a pH of 6.2 and grossly tends to decrease the elevated pH of nasal secretion in the presence of infection."

(Biomydrin is contained in a pliable plastic squeeze bottle with a spray top and thus may be used in the home to be administered as a fine spray which affords the maximum opportunity to insure coverage of the entire mucosal area with a thin layer of drug sufficient to provide the required bactericidal effect.) By inverting the container, "it acts perfectly as a dropping bottle, and may be used as such for ordinary topical application," the doctors reported.

6,000 DOSES OF LIFE-SAVING ANTIBIOTIC, CHLOROMYCETIN, RUSHED BY AIR TO EARTHQUAKE-HIT AREA IN CENTRAL CHILE

In response to an urgent cable, Parke, Davis & Company airexpressed to Santiago, Chile, a gift of 6,000 doses of Chloromycetin for use in the Central Chile area which was hit severely by earthquake May 6.

W. R. Jeeves, vice president and director of overseas operations for the pharmaceutical firm, said the large quantity of the antibiotic was rushed via Pan American World Airways to Dr. Eugenio Suarez of the Ministry of Public Health at Santiago. The Office of International Trade, Department of Commerce, in Washington waived the usual formalities with regard to export licensing so the emergency shipment could be expedited.

Press reports stated the earthquake inflicted heavy damage on two cities, killing at least seven persons and injuring more than 100. The quake was felt from Aconcagua Province, north of Santiago, to the southern tip of Llanquihue Province. Its force was focused in the Concepcion-Chillan area.

Chloromycetin is used by physicians to combat typhoid and other diseases which flare up in disaster areas.

M & R AWARD TO DRS. BLOCK AND DAVIS

The M & R Awards for the two most significant articles to appear in the journal GP during 1952 went to Dr. E. A. Davis of Charleston, West Virginia for his paper "The Art of Ethics of Medicine," and the Dr. Marvin Block of Buffalo, New York for "Alcoholism, the Physician's Duty." Presentation of the awards was made in St. Louis, March 24 by Dr. W. J. Shaw, chairman of the M & R Award Committee of the American Academy of General Practice, during the Academy's fifth annual meeting.

The M & R Award is given each year to the authors of the two papers selected by three deans of medical schools as judges. M & R Laboratories, producers of Similac, sponsor the awards.

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simple!

Convenience of ready-to-use single-dose disposable cartridges for use with the Pfizer Steraject Syringe. Handy for office, house calls and hospitals. Among the widely used antibiotic formulations available are:

Penicillin G Procaine Crystalline in Aqueous Suspension; 300,000 units, 600,000 units, and 1,000,000 units.

Permapen* Aqueous Suspension (brand of dibenzylethylenediamine dipenicillin G): 600,000 units.

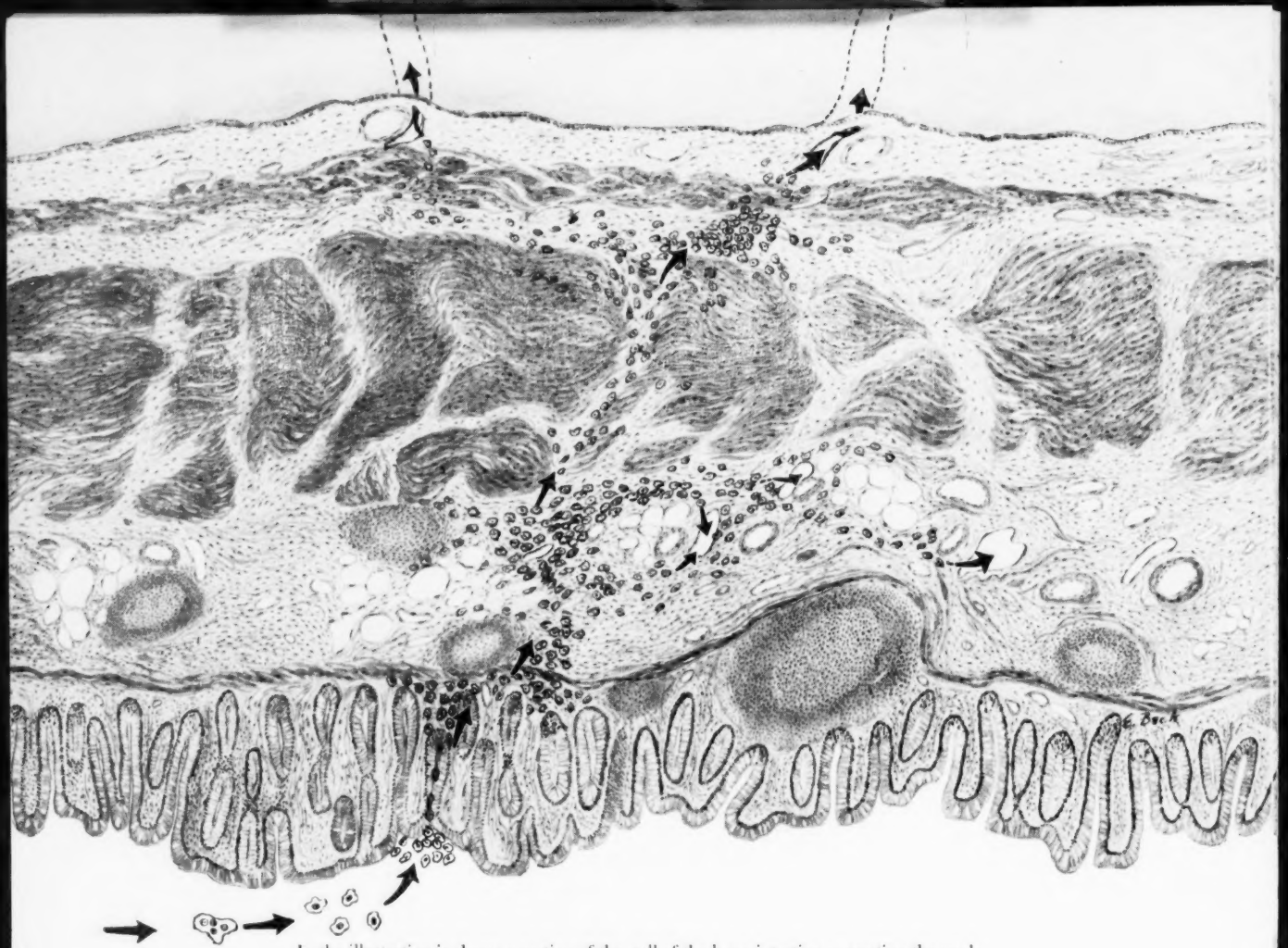
Combiotic* Aqueous Suspension: 400,000 units penicillin G procaine crystalline and 0.5 Gm. dihydrostreptomycin.

Streptomycin Sulfate Solution: 1 Gm.

Dihydrostreptomycin Sulfate Solution: 1 Gm.

Antibiotic Division, CHAS. PFIZER & Co., Inc., Brooklyn 6, N. Y.

*TRADEMARK, CHAS. PFIZER & CO., INC.



In the illustration is shown a section of the wall of the large intestine suggesting the mode of invasion of *Endamoeba histolytica* into the various levels; the mesenteric venules lead to the liver and escape of some of the parasites may cause an amebic abscess of the liver.

Diodoquin® in Amebiasis

"Diodoquin is very effective in curing the intestinal infection...."*

In a recent survey of seven commonly-used amebacides, Weingarten* concluded that Diodoquin (diiodohydroxyquinoline, U.S.P.) gave an excellent percentage of cures with maximal safety for the patient.

The active protozoacidal agent in Diodoquin is iodine, present in the high percentage of 63.9.

As a result of this high iodine content, Diodoquin is extremely potent and, with few exceptions, a twenty-day divided dosage will destroy the offending organisms. This efficient therapeutic effect is due to the high levels of insoluble halogen acting in the lumen of the bowel. It is a well tolerated and relatively nontoxic amebacide.

Diodoquin's simplified dosage plan, three 10-grain tablets daily for twenty days, is a decided improvement for treating both the asymptomatic and symptomatic forms of amebiasis. It is accepted by the Council on Pharmacy and Chemistry of the American Medical Association. Diodoquin is supplied as tablets of 10 grains (650 mg.) in bottles of 60 and 500.

*Weingarten, M.: Proctology Symposium: Amebiasis: Medical Aspects, Mod. Med. *20*:121 (May 15) 1952.

SEARLE *Research in the Service of Medicine*